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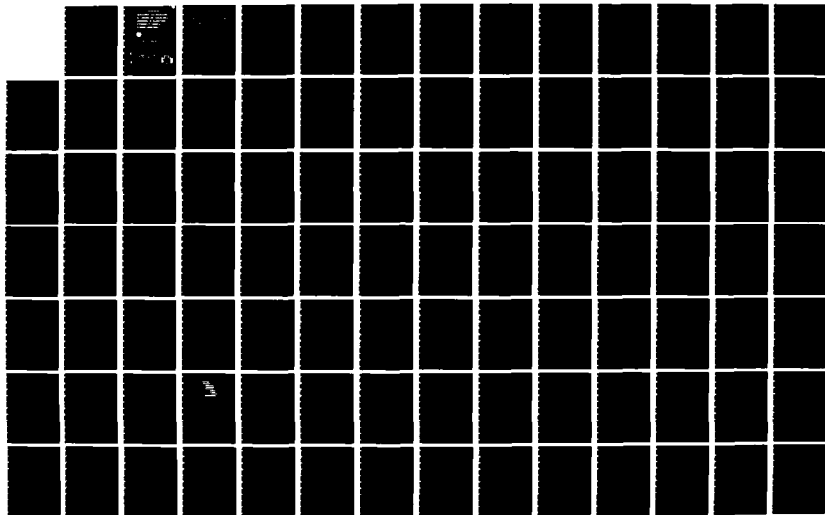   TOXICOLOGICAL ASSESSMENT OF O   (U) SOUTHWEST RESEARCH
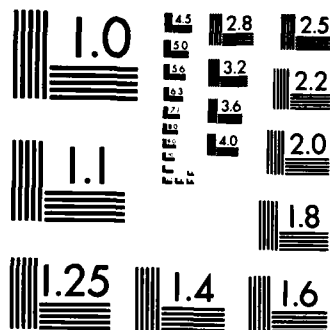   INST SAN ANTONIO TX   H L KAPLAN ET AL   SEP 85   1/3

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DEVELOPMENT AND APPLICATION
OF A METHOD FOR TOXICOLOGICAL
ASSESSMENT OF OCCUPATIONAL
EXPOSURES TO CHEMICALS
IN MARINE OPERATIONS

Harold L. Kaplan
William J. Popielarz
E. John Grandel
Robert L. Rose

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SOUTHWEST RESEARCH INSTITUTE
Post Office Drawer 28510, 6220 Culebra Road
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DEVELOPMENT AND APPLICATION OF A METHOD FOR TOXICOLOGICAL ASSESSMENT OF OCCUPATIONAL EXPOSURES TO CHEMICALS IN MARINE OPERATIONS

By

Harold L. Kaplan
William J. Astleford
R. John Prevost
Robert L. Bass

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16. Abstract

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The objective of this supplemental report was the development and application of a method for toxicological assessment of marine occupational exposures to chemicals. More than 200 exposure samples were evaluated for a wide range of marine work activities including tank loading and discharging, tank gauging, tank entry and cleaning, and various on-deck activities. A two-tiered approach, based on current (ACGIH) Threshold Limit Values, was adopted for toxicological assessment of occupational exposure data. One-half of the ACGIH TLV-TWA value of a chemical was designated as the level of exposure requiring medical monitoring and, possibly, some type of industrial hygiene corrective action. All exposures to workplace concentrations without regard to the exposure duration, equal to or exceeding this medical monitoring response level should require medical monitoring of exposed personnel. Exposures to concentrations greater than the TLV-TWA value should be considered potentially hazardous and should require implementation of industrial hygiene remedial action in addition to the medical monitoring of exposed workers. In the Tier I evaluations, the measured exposure data were screened in order to identify those exposures in which the concentration of chemical equalled or exceeded the medical monitoring response level of the chemical, Those exposures that were equal to or exceeded this level were designated toxicologically significant and requiring further evaluation. In the Tier II evaluations, in-depth toxicological assessments were made of the measured exposure data to ascertain the nature and severity of toxic effects and the degree of hazard anticipated from the exposure.

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EXECUTIVE SUMMARY

Background

The term, "Marine Hazardous Chemical Worker," is used to encompass workers whose activities involve the potential for exposure to hazardous substances. Potential safety hazards from flammable and toxic substances in the work environment are inherent in their job activities. Hazardous substances include vapors, gases, liquids, mists, and dust; and the sources of these substances may be encountered during both routine and nonroutine work situations. The potential for exposure to these substances varies with work functions, operational equipment and procedures. Thus, a simplified definition of hazardous sources, equipment and work practices for marine personnel is not possible. Furthermore, the work schedules do not follow the normal 8-hour day that is characteristic of other industries. Because of this, marine worker exposures are difficult to evaluate in terms of the usual ACGIH and OSHA/NIOSH exposure limit values.

This report supplements the results of Phase II of a two-element USCG research project entitled "Investigation of the Hazards Posed by Chemical Vapors Released in Marine Operations." Over 200 exposure samples were obtained in Phase II for various work activities including single and multiple event exposures during tank entry, tank gauging, and on-deck work activities. A preliminary assessment of marine terminal occupational hazards was given in the Phase II Final Report. This Addendum to the Phase II report analyzes the exposure data in depth.

Toxicological Assessment Objectives

The Phase II results showed that industrial exposure standards are not generally applicable to the marine environment because exposure scenarios and work schedules in the marine environment do not conform to conventional industrial schedules. Consequently, the U. S. Coast Guard must develop and utilize a different approach to assess the toxicological hazards of exposures of marine workers and to establish exposure limit guidelines. Therefore, the

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objective of this supplemental report is the development and application of a method for toxicological assessment of marine occupational exposures to chemicals. The following elements were included in developing and applying this methodology:

° Review of toxicological principles;

° Definition of the marine exposure environment;

° Review and evaluation of applicability of existing chemical exposure guidelines;

° Review and evaluation of applicability of limit value adjustment models;

° Development of proposed methodology;

° Toxicological assessment of Phase II measured exposure data;

° Evaluation of applicability and limitations of proposed methodology.

Chemical Toxicity

Fundamental principles of toxicology, with particular emphasis on those that are relevant to the exposure of workers to chemicals in the marine environment are presented in the report. These principles are then applied to marine chemials and work practices in order to characterize the nature of toxicological hazards in the marine environment.

Toxicants refer only to those chemicals, whether in solid, liquid, vapor or other form, to which marine workers may be exposed during performance of their duties in the marine environment. Toxic chemicals are classified either by chemical structure as, for example, in classifying toxicants as alcohols, aldehydes, aromatics and other chemical groups or on the basis of the organ or system that is the "target" site for the effect of the chemical. In the marine environment, workers are often exposed to mixtures of chemicals which have different chemical structures but act on the same organ or biological system. Therefore, in this report, the toxicants are categorized according to target organ or system as follows:

° Respiratory Systems Toxicants
° Neurotoxicants

- Hepatotoxicants
- Nephrotoxicants
- Cardiotoxicants
- Carcinogens
- Hematopoetictoxicants
- Sensitizing Agents
- Other toxicants - Teratogens/Reproductive Toxicants

Within this context the uptake (inhalation, ingestion, skin absorption), distribution, metabolism and excretion of toxicants are reviewed.

Even when all other factors are strictly controlled, there is still likely to be considerable variation among individuals in their response to a specific toxicant. This variation may be due to factors that influence the absorption, distribution, metabolism or excretion of the chemical or to any of a number of other factors. The major factors that may influence the toxicity of a chemical to an individual, and consequently the hazard of the chemical, are reviewed and include:

- Physical and Chemical Properties
- Environmental Factors
- Host Factors
  - Age
  - Health Status
  - Sex
  - Personal Habits
  - Nutritional Status and Dietary Factors
  - Genetic Status

Biological interactions are also reviewed. The general mechanisms of toxicological interactions are reviewed and the sites and mechanisms of these interactions are discussed.

Marine Operational Exposures and Guidelines

Marine vessels transport a wide variety of chemical substances, some of which are also commonly encountered in the industrial environment. The ACGIH has assigned threshold limit values (TLVs) for exposure of industrial workers to many of these chemicals, based on toxicity data obtained from accidental and occupational exposures and experimental research. However, the exposure conditions during marine operations are considerably different from those in the industrial workplace so that some of these limit values may not be appro-

priate for typical exposures in the marine environment.

Exposure guidelines is a general term that refers to concentrations of atmospheric chemicals in the industrial and occupational environments that are considered "safe" for exposure of individuals for specified times or under specified conditions. Examples of these standards are Theshold Limit Values (TLVs), Permissible Exposure Limits (PELs), Immediately Dangerous to Life or Health Levels (IDLHs) and NIOSH Recommended Standards. This report reviews existing exposure guidelines and their use in the conventional work schedule, examines models for adjustment of the guidelines to unusual work schedules and considers the application of these guidelines and models to the marine environment. Exposure guidelines that are reviewed in this report include ACGIH Threshold Limit Values, OSHA Permissible Exposure Limits, and NIOSH recommended standards. The USCG's authority to set exposure standards for marine workers is also discussed.

The 600+ liquid bulk cargos that are regulated by the USCG under Title 46, Subchapters O and D, of the Code of Federal Regulations are reviewed. The regulated substances range from edible vegetable oils to highly toxic carcinogens. For many of these substances, the health hazard potential has been established by the National Fire Protection Association (NFPA), the National Academy of Sciences (NAS), and the American Conference of Industrial Hygienists (ACGIH). The results of their evaluations are reviewed. A listing of the Subchapter D and Subchapter O substances for which the ACGIH has adopted TLVs is also presented.

The more than 600 chemicals that are regulated in marine transport vary widely in chemical structure and physical and chemical properties. This diversity in structure and properties is reflected in the wide range of toxicities exhibited by these chemicals, which have potential effects on almost every organ or system of the body. Specific examples of a limited number of these chemicals and the target organs affected by each are given. Eleven of the 600 chemicals have been designated carcinogens by ACGIH. These carcinogens are presented, and for each substance, the 8-hour Time Weighted Average (TWA) and the CHRIS (Chemical Hazards Response Information System published by the USCG) code designation are provided. The ACGIH "Skin" notation has also

been included for those substances so designated by ACGIH. In addition to these substances, the carcinogenic potential of certain other substances and mixtures are noted.

Maritime work schedules differ in many ways from the conventional work schedules of land-based industries. These differences range from annual to daily work schedules and include variations that reflect either the operational requirements or established practices on the vessel. The report describes 1) the departure of the maritime work schedule from the conventional 8-hour day, 40-hour week and 2) the potential for occupational exposures during tank ship operations. For some operations an extended work schedule may be necessary. The duration of observed extended work routines ranged from 12 to 30 consecutive hours. Basically, these extended work periods occur as a result of defined responsibility, overtime and shift swapping.

The most important factor that is capable of modifying the toxicity of chemicals in the marine environment is, without doubt, potential biological interaction of certain marine chemicals. This factor assumes this degree of importance primarily because of the nature of work activities during marine operations. Inherent in many of these work activities are the opportunities for simultaneous exposures of personnel to a number of different chemicals or to sequential exposures to different chemicals. As a consequence of such exposures, biological interactions may occur and result in marked alterations of the toxicity of these chemicals to the marine worker. This is reviewed in detail, and while the ACGIH does recommend a formula for evaluating the additive effects of chemicals which act upon the same organ system, this formula is not applicable to the synergistic interactions of chemicals. Consequently, it is not possible to establish allowable concentrations for these chemicals in many simultaneous or sequential exposures of the marine worker. However, it is important to be aware that an apparently nontoxic exposure to a chemical may actually produce toxic effects when biologically interacting chemicals are also present.

In the marine environment, both the traditional and extended work schedules may not permit an adequate reduction of body burden of chemicals and therefore may invalidate TLV-TWA and PEL values. In addition, exposure excur-

sions may frequently exceed acceptable limits because control and monitoring of concentrations, durations and frequency of exposure are not readily accomplished during marine operations. This same limitation of control and monitoring may result in marine exposures that exceed other guidelines such as the TLV-STEL, TLV-C and OSHA ceiling values. Furthermore, these standards, as well as the 8-hour time-weighted averages, may not be applicable to many of the exposures that involve mixtures of chemicals which have interactive effects.

The application of exposure limit values and adjustment models to marine operations are also reviewed in this report. Adjustment of existing exposure limits to reflect maritime exposure conditions appears to be a promising approach to ensure a safe environment for the marine worker. However, present adjustment models have limitations, which are discussed; these models need further development and validation before they can be used for many of the types of exposures encountered during marine operations. For the present, the most prudent approach is the conservative application and interpretation of existing guidelines.

Toxicological Assessment of Measured Exposure Data

The report presents a toxicological assessment of the more than 200 exposure samples that were collected for various work activities.

A two-tiered approach, based on current ACGIH Threshold Limit Values, was adopted for toxicological assessment of the occupational exposure data. One-half of the ACGIH TLV-TWA value of a chemical was designated as the level of exposure requiring medical monitoring and, possibly, some type of industrial hygiene corrective action. All exposures to workplace concentrations without regard to the exposure duration, equal to or exceeding this medical monitoring response level should require medical monitoring of exposed personnel. Exposures to concentrations greater than the TLV-TWA value should be considered potentially hazardous and should require implementation of industrial hygiene remedial action in addition to the medical monitoring of exposed workers. In the Tier I evaluations, the measured exposure data were screened in order to identify those exposures in which the concentration of chemical equalled or

exceeded the medical monitoring response level of the chemical. Those exposures that were equal to or exceeded this level were designated toxicologically significant and requiring further evaluation.

In the Tier I screening process, many of the measured occupational exposures were below the medical monitoring response level concentrations. Some exposures, however, equalled or exceeded this level, and these exposures were further evaluated in Tier II assessments. In accordance with guidelines promulgated in the USCG Occupational Medical Monitoring Manual, COMDTINST M6260.15, dated 11 January 1983, an exposure meets the criterion for an occupational exposure for medical monitoring purposes if the concentration of the chemical(s) equals or exceeds 50 percent of the TLV-TWA for the chemical or mixture of chemicals.

In the Tier II evaluations, in-depth toxicological assessments were made of the measured exposure data to ascertain the nature and severity of toxic effects and the degree of hazard anticipated from the exposure. These assessments were based primarily on human toxicity data obtained from accidental and industrial exposures, but relevant experimental animal data were also used in the case of some chemicals, when human data were not available or limited. In addition, factors unique to the marine environment were also considered in applying these human and animal data to the measured exposures.

It is apparent from the toxicological assessments of the measured exposures that the marine environment is potentially hazardous. Unprotected crewmen were exposed to chemicals some of which are regarded as highly toxic and have the potential to cause serious damage to several organs and systems of the body. Examples of these chemicals are n-hexane, epichlorohydrin, ethylene dichloride, benzene, carbon tetrachloride and chloroform. Human epidemiologic and experimental animal data indicate that the latter three chemicals may be carcinogenic to man. In many of the measured exposure scenarios, concentrations of all chemicals were very low, and the exposures do not meet the medical monitoring response level criterion. In other situations, however, the concentrations were sufficiently high so as to warrant medical monitoring of exposed personnel. In some cases, particularly those involving tank entry and open tank gauging, the measured concentrations exceed

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ACGIH and TLV-TWA values and are considered potentially hazardous. The potential hazards of such exposures may be increased by certain unique conditions of marine operations such as 1) extended work schedules, 2) sequential or simultaneous exposures to a number of chemicals having interactive effects, and 3) stress.

Toxicological Assessments of Hypothetical Exposure Scenarios and Data

Toxicologic assessments were also made on a number of hypothetical exposure scenarios that involved combinations of work activities in which measured data were obtained. Although more than 200 exposure samples were collected during these work activities, these measured data represent only a small fraction of the chemicals involved in marine operations. Therefore, the measured exposure data were supplemented with hypothetical but realistic exposure predictions for certain operating conditions.

The same conservative two-tiered approach that was used for the measured occupational exposure data was also followed in assessing the hypothetical exposure sequences. Hypothetical exposure data are presented and evaluated for tankship operations. The data for the first three categories of operations (open gauging, deck work downwind of tank loading and tank entry) represent realistic predictions based on certain assumed operating conditions, the physical properties of the applicable chemicals, and analytical computer models of tank ventilation and plume dispersion. For the fourth operation which involved tank washing, entry and cleaning, documented work activities were used in combination with assumed chemicals with potential for dermal absorption.

From the toxicological assessments of the hypothetical data, it is apparent that many of the work sequences would result in hazardous exposures of crewmen. Under certain assumed (but realistic) conditions, the predicted concentrations of certain chemicals greatly exceeded Threshold Limit Values. In some instances, the levels were sufficiently high to cause serious toxic effects in exposed crew members. These assessments of hypothetical data emphasize the need for the use of proper protective equipment and clothing by marine personnel as well as for a maritime medical and environmental monitoring program.

Conclusions

Industrial exposure guidelines based on a conventional 8-hour work day, 40-hour work week, are not directly applicable to chemical exposures encountered during marine operations. Present limit value adjustment models also have limitations in their application to marine operations. Therefore, it was necessary to develop a practical method, based on industrial exposure limit values, to evaluate the toxicological hazards of exposure to chemicals by marine workers. Specifically, an exposure concentration level of (TLV-TWA)/2 was selected as a level to identify toxicologically significant exposure. Roughly, 200 exposure samples were collected and evaluated. These samples represent a wide range of activities, including tank loading and discharging, tank gauging, tank entry and cleaning, and various on-deck activities. In addition, 1) measured exposures were combined into hypothetical exposure sequences and 2) hypothetical, but realistic, exposures were mathematically predicted for additional chemicals and selected work activities in order to provide a more comprehensive evaluation of the marine environment. Toxicological assessments were made of the measured and hypothetical exposure data and the following conclusions were reached:

°   The two-tiered approach that was developed is a conservative and practical method for toxicological evaluation of exposures of maritime workers to chemicals. The Tier I evaluation readily differentiates between exposures that are not of toxicological significance (exposure concentrations <TLV-TWA/2) and those exposures that are of significance. The Tier II evaluation provides an assessment of the potential toxicity and hazard of those exposures that are toxicologically significant.

°   It is apparent from the evaluations of both the measured and the predicted exposure data that the marine environment is a toxicologically hostile environment. Under certain conditions, concentrations of chemicals may be sufficiently high to cause marked toxic effects in exposed marine workers.

°   Host factors and environmental/work conditions unique to marine operations may potentiate the toxicity of chemicals in the marine environment.

°   In marine operations, the potential exists for exposure to chemicals that are suspect human carcinogens. In certain work activities, concentrations of these chemicals did or may considerably exceed the medical monitoring response level.

° During tank entry and open tank gauging, there is an enhanced potential for exposure to hazardous concentrations of chemical vapors.

° In contrast to industrial exposures for which considerable epidemiological, accidental exposure, and experimental exposure data exist for many chemicals, there are insufficient data to predict the effects of marine environmental/work conditions and host factors on the toxicity of chemicals.

° There are insufficient epidemiological data relevant to the development of cancer among marine workers to estimate the hazards of repetitive, sequential and simultaneous exposures to carcinogenic chemicals in marine operations.

° Because the marine environment is a toxicologically hostile and hazardous environment, the need exists to control and reduce exposures of marine workers to chemicals and to monitor their health status.

Recommendations

Corrective measures are needed to reduce observed occupational vapor exposures in the marine work environment. This corrective action will require implementation of a marine occupational safety and health program which includes an effective industrial hygiene program to control, reduce, and monitor exposure levels, and an adequate medical monitoring program to serve as a safety net. Once these measures are in place, continuing toxicological assessment, using the procedures outlined in this report, would be needed to evaluate the effectiveness of the corrective measures implemented and to recommend modifications, if needed.

The occupational safety and health program recommended to reduce toxicological hazards in the marine work environment would include the following elements:

° Development and implementation of appropriate engineering controls to reduce workplace concentrations;

° Develop and use of safe work practices;

° Determination and provision of appropriate protective gear;

° Provision of adequate training and education regarding handling of toxic chemicals;

° Routine monitoring of environmental concentrations in confined spaces before entry;

° Establishment of routine industrial hygiene survey audits of standard work practices;

° Consideration of biological monitoring methods for appropriate chemical substances and work activities; and

° Establishment of medical monitoring, at specified intervals, of all personnel potentially exposed to toxic chemicals in their routine duties.

Specific recommendations for certain elements of the marine safety and health program are also presented in this report.

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I. INTRODUCTION

I.1 Statement of the Problem

I.1.1 Marine Tanker/Barge Operations

One of the important functions of the marine industry is the transportation of bulk liquid products. Bulk liquid cargos include pure chemicals, gasoline, crude oil and other common chemical or petrochemical products transported in tank ships or barges. Transport and handling of these liquid cargos involve a variety of operations where exposure to cargo vapors and liquids may be encountered. Cargo tanks often require washing and gas freeing prior to loading. After machine cleaning, tanks are usually entered for manual cleaning and/or inspection. Prior to cargo transfer, product hoses from a marine terminal or another vessel are often manually connected over open manifold drip trays. The manifolds are designed to handle several product hoses simultaneously and direct the product, or products, to specified tanks aboard the vessel. During cargo loading, tanks may be manually gauged and, for most products, vapors are vented to the atmosphere while various work activities proceed downwind of the open vents. After loading is complete, hoses containing residual product are disconnected, drained and stowed or returned to the marine terminal.

Although there are many similarities in tank ship and barge activities, there are also important differences. On tank ships, tanks emptied during product discharge often require immediate cleaning to prepare the tank for refilling in the same port or marine terminal. Tank cleaning and maintenance activities are otherwise usually scheduled to occur while the ship is underway between ports. Empty tanks are sometimes ballasted which requires discharge prior to cleaning and reloading operations. The discharged ballast will carry some residue of the product previously carried by the tank. In barge operations, tank cleaning and maintenance are usually accomplished at a shipyard or barge washing facility rather than by barge or towing personnel. Because of these operational differences and because barge personnel do not live aboard the barges, the activities of barge personnel usually differ somewhat from those of tank ship personnel.

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In the performance of tanker operations, the traditional work schedule consists of 4-hour watches separated by 8-hour rest periods, seven days per week. A variation in this schedule is the 6-hous-ON, 6-hours-OFF routine. At times, such as approaching a marine terminal for tie up or when casting off to leave a terminal and proceed underway, all hands are called to the deck, regardless of watch. At other times, when cargo transfer activities are particularly demanding, watches are extended to twelve, sixteen or even twenty-four hours. On the other hand, barge tankermen tend to continuously follow cargo transfer operations from beginning to end. In this case, there is no repetitive work schedule.

I.1.2 Exposure of Marine Personnel

During the various marine operations, the potential exists for exposure of personnel to one or more of a large number of chemicals. Exposure may occur during activities on the open deck or in enclosed areas such as cargo tanks, pumproom, engine room, and deck house. Deck house and engine rooms can be infiltrated by cargo vapors through the ventilation systems as well as through open access doors during loading, tank cleaning and ballasting of cargo tanks.

Exposure can occur by inhalation of the chemical vapors, and, during certain work activities such as product sampling, hose hookup/disconnect, and tank entry, chemicals may come in contact with the skin of personnel and cause local reactions or be absorbed through the skin into the body. It is also possible for food or cigarettes to become contaminated from chemicals on the hands of workers, and these chemicals may then enter the bloodstream via the digestive tract.

Depending on his activities and the particular chemical cargos on the vessel, a worker may be exposed to a single chemical or to a mixture of chemicals. In the case of a single chemical, the exposure may occur only once as, for example, during entry into one tank containing residual chemical. If entry is made sequentially into a number of tanks containing residue of the same chemical, repetitive or sequential exposures to that chemical may result, with intervening periods without exposure. Entries into tanks containing

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different chemical residues may result in sequential exposure of workers to several chemicals. Exposures to a number of chemicals may also occur simultaneously as, for example, on deck during the loading and venting of several cargo tanks. Such exposures may also be repetitive or sequential, with subsequent exposures to the same or different mixtures of chemicals occurring after varying periods of non-exposure.

I.1.3 Occupational Exposure Standards

Governmental agencies and other organizations such as the Occupational Safety and Health Administration (OSHA), the National Institute of Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (ACGIH) and private industries have been concerned with the safety and health of the industrial worker for many years. As a result of the efforts of these organizations, standards in the form of exposure limits have been established for most chemicals encountered in the industrial environment. These exposure limits are generally time-weighted average exposure values based on the traditional industrial eight-hour work day, with intervening 16-hour non-exposure periods, five days per week. These industrial exposure limit values are usually not directly applicable to the exposures encountered during marine operations because the work schedules of marine workers often differ considerably from the conventional industrial work schedule. However, in the absence of marine specific exposure limits, these industrial exposure limit values can be used as guidelines.

I.2 Objective and Approach

I.2.1 Objective

The United States Coast Guard has broad responsibility for the safety and health of workers on U. S. flag vessels and is concerned with the health of marine personnel exposed to chemicals. Consequently, the Coast Guard is conducting research programs to identify and characterize potentially hazardous safety and health situations in the marine environment. One of these programs is designed to measure the exposure of marine workers during various operations, develop models for predicting exposures during work activ-

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ities and assess the toxicological hazards of exposure to chemicals in the marine environment.

Industrial exposure limits are not directly applicable to the marine environment because work schedules in the marine environment do not conform to conventional industrial schedules. Therefore, the U. S. Coast Guard must develop and utilize a different approach to assess the toxicological hazards of exposures of marine workers and to establish exposure limit guidelines. It is the objective of this document to develop an approach for hazard assessment of marine worker exposures to chemicals for utilization by the U. S. Coast Guard.

I.2.2 Approach

An approach to hazard assessment of exposure of marine workers to chemicals has been developed and is presented in this document. The following sequence was followed in developing this approach:

1) Review of toxicological principles,

2) Review of existing exposure guidelines,

3) Definition of the marine exposure environment,

4) Review and evaluation of applicability of limit value adjustment models, and

5) Development of a two-tiered approach for toxicological assessment of occupational exposures.

The two-tiered approach was then applied and evaluated in the following sequence of activities:

1) Toxicological assessment of measured exposure data,

2) Toxicological assessment of hypothetical exposure data, and

3) Evaluation of applicability and limitations of the approach.

The presentation of information in this report follows the same sequence as that outlined above for development, application, and evaluation of the approach.

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II. TOXICITY OF CHEMICALS

II.1 Introduction

The purpose of this section is to review certain fundamental principles of toxicology, placing particular emphasis on those that are relevant to the exposure of workers to chemicals in the marine environment. In subsequent sections, these principles will be applied to marine chemicals and work practices in order to characterize the nature of toxicological hazards in the marine environment.

II.2 Classification of Toxicants

II.2.1 Introduction

All chemicals, in sufficient quantities, are toxic; that is, all chemicals have the potential of producing adverse effects on a living organism. However, the terms "toxic," "toxicity" and "toxicant" are usually restricted in use to chemical agents which, under usual circumstances or conditions, are capable of producing deleterious effects, seriously injuring body functions or destroying life. Thus, in this document, toxicants refer only to those chemicals, whether in solid, liquid, vapor or other form, to which marine workers may be exposed during performance of their duties in the marine environment.

It is common to classify or group toxic chemicals in some manner because of their large number and wide diversity in chemical structure and toxic effects. One approach is by chemical structure as, for example, in classifying toxicants as alcohols, aldehydes, aromatics and other chemical groups. Another common classification is based on the organ or system that is the "target" site for the effect of the chemical. In the marine environment, workers are often exposed to mixtures of chemicals which have different chemical structures but act on the same organ or biological system. Therefore, in the following review of types of toxicants, the toxicants are categorized according to target organ or system. Although specific examples of chemicals are given for each category, the reader should realize that many chemicals act

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on a number of organs or biological systems and can be included in more than one toxicant category.

II.2.2   Respiratory System Toxicants

Many of the chemicals encountered in the occupational environment are capable of producing irritant effects to the respiratory system, and some cause more severe and permanent damage. The term "irritant" is generally used to refer to chemical gases, vapors and dusts which produce inflammation in surface tissues in which they come in contact. These tissues include the skin, the conjuctiva of the eyes and the membranes of the mouth and respiratory tract. When some of the irritant chemicals, in concentrated liquid form, come in contact with tissues, they are caustic and corrosive, causing chemical burns at the site of contact. Irritants are often differentiated as primary or secondary irritants on the basis of their systemic toxicity. A primary irritant is defined as one that exerts no sytemic toxic action or one whose irritant action in the resiratory tract far exceeds any systemic toxic effect. Examples of these chemicals are hydrochloric acid, sulfuric acid and mustard gas. Secondary irritants, in contrast, exert an irritant action on mucous membranes but produce a far more significant systemic effect resulting from the absorption of the chemical. Generally, these chemicals produce irritant effects at lower concentrations, and considerably higher concentrations are necessary for systemic toxic effects. Many of the aromatic hydrocarbons and other organic compounds which are commonly transported in the marine industry are secondary irritants.

Alarie (1) has differentiated irritants on the basis of their site of action as sensory irritants, pulmonary irritants, bronchoconstrictors and respiratory irritants. One of the more important factors in determining the site of action of a chemical within the respiratory tract is the solubility of the chemical. Sensory irritants are highly soluble and affect primarily the upper respiratory tract. When inhaled, these chemicals stimulate the trigeminal nerve endings of the nose, evoke a burning sensation and inhibit respiration. Most will also produce laryngeal stimulation and coughing. Sensory irritants are also capable of stimulating trigeminal nerve endings of the cornea and inducing tearing and, at higher concentrations,

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causing a burning sensation in the skin. Typical examples of this irritant group are chloroacetophenone, acrolein, ammonia, hydrogen chloride and sulfur dioxide.

Pulmonary irritants are less soluble than sensory irritants and penetrate more deeply into the respiratory tract. These chemicals, when inhaled, stimulate sensory receptors within the lungs and increase respiratory rate, with a decrease in tidal volume, resulting in rapid shallow breathing. Their action causes a sensation of dyspnea (labored breathing) and breathlessness, rather than a conscious painful sensation which is characteristic of the sensory irritants. Also, pulmonary edema may develop, which is then accompanied by painful breathing. Pulmonary irritants cause little or no irritation of the eye or nasal passages at concentrations sufficient for pulmonary irritation and, therefore, provide little warning of their presence. Typical examples of pulmonary irritants are phosgene, nitrogen dioxide, sulfuric acid mist, ozone and arsenic trichloride.

Bronchoconstrictors refer to those chemicals which, when inhaled, induce an increase in resistance to airflow within the conducting airways of the lung. This action may be produced by a direct effect on the smooth muscles of the conducting airways, the reflex stimulation of nerve endings or the liberation of histamine. Most of these chemicals are also sensory irritants and their action on the bronchial mucosa produces a painful sensation. Sulfur dioxide, ammonia and toluene diisocyanate are examples of this group of irritants.

Some chemicals, when inhaled, can act as a sensory irritant, a pulmonary irritant and a bronchoconstrictor. Irritants capable of all three actions are referred to by the general term of "respiratory irritant." Examples are chlorine, dichloromethyl ether and chloropicrin.

In addition to irritation, a number of occupational chemicals are capable of causing other effects to the respiratory system, sometimes resulting in serious disease conditions. Menzel and McClellan (2) have categorized effects of these toxicants of the respiratory system into the following five general categories of damage or response:

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1. Irritation of the air passages, causing constriction of the airways and often accompanied by edema and secondary infection.

2. Damage to cells lining the airways, resulting in necrosis, increased permeability and edema.

3. Fibrosis which may become massive and cause obliteration of the respiratory capacity of the lung. Local fibrosis of the pleura also occurs, restricting movement of the lung and causing irritation of the pleural surfaces and pain.

4. Constriction of the airways through allergic responses.

5. Oncogenesis leading to primary lung tumors.

In Table II-1 are listed several important occupational chemicals with their sites of action and the pulmonary effects or diseases they produce. Many of these agents produce an acute effect from short exposures to high concentrations and chronic effects after long-term exposures to lower concentrations.

II.2.3   Neurotoxicants

One of the most important groups of toxicants consists of those chemicals which act on the central or peripheral nervous systems, i.e., the neurotoxicants. Many of the chemicals that have been included in this category also have significant effects on other organs and systems and may be designated primarily as, for example, hepatotoxicants or nephrotoxicants. However, for the purpose of this document, any chemical which has the capability of altering nervous system function is considered a neurotoxicant.

The neurotoxicants are particularly significant in the occupational environment because of both the large number of occupational chemicals capable of producing neurotoxic effects and the potential seriousness of these effects. This capability is not limited to chemicals with a particular chemical structure but, rather, is characteristic of several classes of chemical compounds. For example, alcohols, hydrocarbons, aromatics and ketones are all major chemical classes having member chemicals with potential effects on the nervous system. Acute exposure to many of these chemicals generally produces

TABLE II-1. SITE OF ACTION AND PULMONARY DISEASE PRODUCED BY SELECTED
OCCUPATIONALLY INHALED TOXICANTS (2)

TOXICANT	COMMON NAME OF DISEASE	SITE OF ACTION	ACUTE EFFECT	CHRONIC EFFECT
Asbestos	Asbestosis	Parenchyma		Pulmonary fibrosis, pleural calcification, lung cancer, pleural mesothelioma
Aluminum	Aluminosis	Upper airways, alveolar interstitium	Cough, shortness of breath	Interstitial fibrosis
Aluminum abrasives	Shaver's disease, corundum smelter's lung, bauxite lung	Alveoli	Alveolar edema	Fibrotic thickening of alveolar walls, interstitial fibrosis and emphysema
Ammonia		Upper airway	Immediate upper and lower respiratory tract irritation, edema	Chronic bronchitis
Arsenic		Upper airways	Bronchitis	Lung cancer, bronchitis, laryngitis
Beryllium	Berylliosis	Alveoli	Severe pulmonary edema, pneumonia	Pulmonary fibrosis, progressive dyspnea, interstitial granulomatosis, cor pulmonale
Boron		Alveolus	Edema and hemorrhage	
Cadmium oxide		Alveolus	Cough, pneumonia	Emphysema, cor pulmonale
Carbides of tungsten, titanium, tantalium	Hard metal disease	Upper airway and lower airway	Hyperplasia and metaplasia of bronchial epithelium	Fibrosis, peribronchial and perivascular fibrosis
Chlorine		Upper airways	Cough, hemoptysis, dyspnea, tracheobronchitis, bronchopneumonia	
Chromium (VI)		Nasopharynx, upper airways	Nasal irritation, bronchitis	Lung tumors and cancers
Coal dust	Pneumoconiosis	Lung parenchyma, lymph nodes, hilus		Pulmonary fibrosis
Coke oven emissions		Upper airways		Tracheobronchial cancers
Cotton dust	Byssinosis	Upper airways	Tightness in chest, wheezing, dyspnea	Reduced pulmonary function, chronic bronchitis
Hydrogen fluoride		Upper airways	Respiratory irritation, hemorrhagic pulmonary edema	
Iron oxides	Siderotic lung disease: Silver finisher's lung, hematite miner's lung, arc welder's lung	Silver finisher's: pulmonary vessels and alveolar walls; hematite miner's: upper lobes, bronchi and alveoli; arc welder's; bronchi	Cough	Silver finisher's: subpleural and perivascular aggregations of macrophages; hematite miner's: diffuse fibrosis-like pneumoconiosis; arc welder's: bronchitis
Kaolin	Kaolinosis	Lung parenchyma, lymph nodes, hilus		Pulmonary fibrosis
Manganese	Manganese pneumonia	Lower airways and alveoli	Acute pneumonia, often fatal	Recurrent pneumonia

(continued)

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TABLE II-1. SITE OF ACTION AND PULMONARY DISEASE PRODUCED BY SELECTED
            OCCUPATIONALLY INHALED TOXICANTS (2) (Continued)

TOXICANT	COMMON NAME OF DISEASE	SITE OF ACTION	ACUTE EFFECT	CHRONIC EFFECT
Nickel		Parenchyma (NiCO), nasal mucosa (Ni_2S_3), bronchi (NiO)	Pulmonary edema, delayed by 2 days (NiCO)	Squamous cell carcinoma of nasal cavity and lung
Osmium tetraoxide		Upper airways	Bronchitis, bronchopneumonia	
Oxides of nitrogen		Terminal respiratory bronchi and alveoli	Pulmonary congestion and edema	Emphysema
Ozone		Terminal respiratory bronchi and alveoli	Pulmonary edema	Emphysema
Phosgene		Alveoli	Edema	Bronchitis
Perchloroethylene			Pulmonary edema	
Silica	Silicosis, pneumoconiosis	Lung parenchyma, lymph nodes, hilus		Pulmonary fibrosis
Sulfur dioxide		Upper airways	Bronchoconstriction, cough, tightness in chest	
Talc	Talcosis	Lung parenchyma, lymph nodes		Pulmonary fibrosis
Tin	Stanosis	Bronchioles and pleura		Widespread mottling of x-ray without clinical signs
Toluene		Upper airways	Acute bronchitis, bronchospasm, pulmonary edema	
Vanadium		Upper and lower airways	Upper airway irritation and mucus production	Chronic bronchitis
Xylene		Lower airways	Pulmonary edema	

symptoms that range in severity, depending on the concentration and duration of exposure, from lightheadedness to prostration and unconsciousness and, finally, to death. Even at the lower concentrations, the less severe effects on the nervous system are important because they may interfere with normal mental and motor functions of an individual and cause impaired performance and accidents.

Although the nervous system is vulnerable to many chemicals, there are two features of this system which provide protection against foreign chemicals. The first feature is the blood-brain barrier which prevents many foreign chemicals from reaching the brain and thereby protects the central nervous system (CNS). In the peripheral nervous system (PNS), a blood-neural barrier is present in some places and absent in others. Not all chemicals are excluded from the brain. Nonpolar, lipid-soluble compounds usually penetrate

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the blood-brain barrier, while highly polar substances are generally excluded. Those toxicants which can penetrate the barrier do not affect all of the several cell types in the brain equally. The different areas of the brain usually exhibit different sensitivities to toxicants as a result of differences in cell biochemistry and in vascularity of the different areas. These differences are integrally related to the diversity of structure and function of different areas of the brain.

The second protective feature of the nervous system is its redundancy of structure, which may mask functional changes until the damage exceeds the reserve capacity of the system. Also, the nervous system can develop tolerance or adapt to some types of damage. Thus, nervous function may return to normal during continuous exposure to a toxic substance. As a consequence, damage to the nervous system may exist and be detectable by cytologic or neurochemical methods when functional damage is not evident. However, at times, changes in function, such as alterations in gait, visual-motor performance, emotional state and other behavioral parameters, may be the earliest and most sensitive indicators of nervous system toxicity.

A number of classification systems has been proposed for neurotoxicants (3, 4). For example, toxicants may be classified according to nervous system function into those affecting 1) sensory functions, 2) motor functions, 3) integrative functions and 4) emotional responses. Toxicants which affect sensory functions may cause damage to the senses of sight and hearing, alterations in the sensations of temperature, touch and pain and other paresthesias. Lead encephalopathy and organic mercury poisoning, as examples, may result in marked sensory damage, including blindness and hearing loss. Motor dysfunction may occur when a toxicant causes demyelination of nerve fibers or neuronal damage. When damage occurs to motor nerve axons or terminal muscles, weakness or paralysis of the involved muscles may result. Inorganic lead salts, organophosphorous compounds and certain industrial solvents (n-hexane, methyl n-butyl ketone) cause disturbances of motor as well as sensory functions. Integrative processes, which are important functions of information processing by the brain, can be the functions that are primarily altered by some neurotoxicants. Various tests have been used to detect alterations in integrative processes such as memory, discrimination and learning in

animals and man exposed to neurotoxicants (5). Emotional behavior may also be altered as a result of exposure to certain neurotoxicants, including inorganic mercury, carbon monoxide and lead. The earliest signs of toxicity in individuals exposed to low levels of inorganic mercury are apprehension, lability and irritability. In the case of acute exposure to carbon monoxide, loss of memory, depression and emotional instability may persist for several weeks in those who survive the exposure.

Another system of classification is based on the primary toxic action or site of damage of the neurotoxicant. Those drugs or chemicals, such as barbiturates and carbon monoxide, which produce effects on the nervous system by causing anoxia comprise one group of neurotoxicants. A second group includes agents that selectively damage the myelin-forming cells in the central and peripheral nervous systems. Examples of these agents are hexachlorophene, lead, thallium and tellurium. Children are particularly susceptible to lead encephalopathy, and severe cases result in permanent cerebral damage (6). Acute thallium poisoning in humans is relatively rare; however, at one time thallium salts were used to produce depilation and resulted in numerous cases of paralysis (7). Neurologic signs of poisoning with this chemical include ataxia, painful paresthesia, leg weakness and diminished sensation.

Chemicals which cause peripheral neuropathies represent a particularly important group of neurotoxicants in the occupational environment because several are industrial chemicals. These agents cause damage to the peripheral motor nerves either by their direct toxic effects on nerve cell bodies, axons and terminations at the myoneural junction or by their demyelinating effects. The neuropathies may develop after a prolonged exposure, as following chronic intake of ethyl alcohol, or after a single exposure, as with triorthocresylphosphate and other neurotoxic organophosphates. In either case, the neuropathy has a delayed onset, and, in the case of the organophosphates, more than a week may elapse before the onset of signs of toxicity, following an acute exposure. Other important members of this group of neurotoxicants are acrylamide, carbon disulfide, n-hexane and methyl n-butyl ketone. Exposure to acrylamide may occur by dermal absorption, inhalation or oral ingestion and may result in polyneuritis in man, with sensory changes in the limbs, weakness and ataxia (8). Chronic exposure to carbon disulfide has

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been reported to produce polyneuritis in 88 percent of intoxicated individuals, including lower-extremity weakness and paresthesias (9). The solvents, n-hexane and methyl n-butyl ketone, which have been used in glues and cleaning fluids and in the manufacture of shoes and printed fabrics, have been responsible for serious neuropathies in chronically exposed industrial workers. Both chemicals are metabolized in the body to 2,5-hexanedione which has been shown to be the neurotoxic agent.

Other neurotoxicants are classified into three additional groups by their toxic effects on either the cell bodies (perikarya) of peripheral neurons, the neuromuscular junctions of motor nerves, or localized anatomic areas in the CNS. Chemicals in these groups are primarily drugs, insecticides and various toxins (botulinum toxin, tetrodotoxin, saxitoxin), although organomercury and inorganic mercury compounds also cause damage to one or more of these sites.

II.2.4   Hepatotoxicants

The term "hepatotoxicant" is used in this document to refer to hepatotoxic chemicals, i.e., chemicals that produce injury to the liver. Injury to the liver as a result of chemical exposure can manifest itself morphologically in different ways (10). The acute effects may consist of an accumulation of lipids (fatty liver) and/or degenerative changes resulting in the death of liver cells (necrosis). The necrotic process may involve small groups of isolated parenchymal cells, groups of cells in zones or all of the cells within an hepatic lobule. The accumulation of lipids may also be restricted to zones of the liver or may be more widespread. Whereas some chemicals (halogenated hydrocarbons such as carbon tetrachloride and chloroform) can produce both necrosis and fat accumulation, others do not. For example, tannic acid and thioacetamide produce lobular necrosis without fat accumulation and ethionine causes a fatty liver with little or no necrosis. Examples of acute hepatotoxic chemicals and their potential to produce necrosis and/or fat accumulation are shown in Table II-2. In contrast to acute effects, injury to the liver from chronic exposure to chemical agents may consist of marked alterations of the entire liver structure with the progressive development of degenerative and proliferative changes (cirrhosis). Neoplastic changes may also occur as a result of liver injury from chronic exposure to certain chemicals.

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TABLE II-2. EXAMPLES OF ACUTE HEPATOTOXIC CHEMICALS (10)

Chemical	Produces Necrosis	Produces Fatty Liver
Carbon tetrachloride	X	X
Chloroform	X	X
Trichloroethylene	X	X
Tetrachloroethane	X	X
Bromobenzene	X	
Dimethylnitrosamine	X	X
Dimethylaminoazobenzene	X	X
Thioacetamide	X	
Pyrrolizidine alkaloids	X	X
Aflatoxin	X	X
Penicillum islandicum	X	X
Amanita phalloides	X	
Tannic acid	X	
Phosphorus	X	X
Ethionine		X
Azaserine	X	X
Cycloheximide		X
Tetracycline		X
Cerium		X
Beryllium	X	
Allyl alcohol	X	
Allyl formate		X
Ethanol		X
Methotrexate		X
Mithramycin	X	
Mitomycin C		X
Puromycin		X
Urethane	X	
Galactosamine	X	X
Acetaminophen	X	
Phenacetin	X	
Furosemide	X	
Emetine		X

A number of systems has been proposed for classifying hepatic injury. For example, Popper and Schaffner (11) differentiated chemical-induced hepatic injury on the basis of the morphologic changes produced by the chemical. More recently, a system based on the mechanism of action of the agent in causing the liver injury was proposed (12). However, except for carbon tetrachloride which has been studied for more than 50 years, the amount of information available on the hepatotoxic mechanisms of chemicals is rather

limited. These mechanisms may involve alterations in lipid metabolism, effects on protein synthesis, cholestatic reactions, lipid peroxidation reactions, necrosis, cirrhosis or carcinogenesis. In the case of fatty livers resulting from chemical exposure, abnormal amounts of lipid, predominantly in the form of triglycerides, accumulate in the parenchymal cells. This accumulation is the result of an imbalance between the rate of synthesis and the rate of release of triglyceride by the cells into the systemic circulation. Any of several mechanisms may be responsible for the imbalance. Recently, it has been shown that a blockage of the secretion of hepatic triglyceride into the plasma is the basic mechanism underlying the fatty liver induced in the rat by carbon tetrachloride (13).

Alterations in protein synthesis by liver cells is another mechanism proposed for hepatic injury caused by certain chemicals. Ethionine, dimethylnitrosamine, carbon tetrachloride, thioacetamide and galactosamine have all been shown to inhibit protein synthesis in the liver. It has been claimed by Mizrahi and Emmelot (14) that dimethylnitrosamine probably affects protein synthesis by causing a loss of messenger RNA from the polyribosomes. Carbon tetrachloride was also found to inhibit protein synthesis but the mechanism of this inhibition has not been determined. Studies have shown a marked reduction of incorporation of amino acids into lipoproteins as well as into hepatic proteins, albumin and fibrinogen (15, 16). The inhibition of protein synthesis is hypothesized by some investigators to be the cause of liver necrosis produced by certain hepatotoxic agents (10). This hypothesis is based on microscopic observations of early changes characteristic of protein inhibition after administration of many of the hepatotoxic chemicals that produce necrosis. However, certain chemicals such as ethionine and cycloheximide inhibit protein synthesis without inducing liver necrosis. In fact, Farber (17) has reported that cycloximide pretreatment protects against hepatic necrosis induced by carbon tetrachloride and against acute necrosis of the biliary epithelium following administration of a-naphthylisothiocyanate.

A number of structurally unrelated drugs (anabolic steroids, phenothiazine derivatives, tricyclic antidepressants, antimicrobial agents) and manganese compounds produce toxic effects characterized by intrahepatic cholestasis (10). This effect has not been associated with exposure to occu-

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pational hepatotoxic chemicals. The important pathologic features associated with the response are bile stasis, bile plugs in the cannaliculi, dilatation of the canaliculi with loss of microvilli and focal necrosis. With the reduction or cessation of bile, there is an ensuing retention of bile salts and bilirubin. The jaundice, resulting from retention of bilirubin, resembles that produced by extrahepatic biliary obstruction. Although mechanisms have been proposed for the cholestasis induced by different drugs, the experimental results on which these mechanisms are based are not definitive (18). In fact, considerable controversy still exists over whether phenothiazines and tricyclic antidepressants cause cholestasis in humans because of a direct toxic effect or because of a hypersensitivity reaction.

Necrosis and cirrhosis are two common morphologic alterations induced by a number of hepatotoxic chemicals. Despite the extensive research and great advances in understanding the morphologic and biochemical alterations associated with chemical-induced liver injury, it has still not been established which of the changes lead to cell death and which are secondary disturbances (10). Farber (17) has suggested that necrosis of cells may not be a degenerative phenomenon but, instead, may be the result of a more active process, as, for example, the overproduction of some enzyme. Whereas necrosis may be an acute or chronic change, cirrhosis is a chronic morphologic alteration of the liver. In animals, a cirrhotic liver can be induced by chronic administration of carbon tetrachloride, aflatoxin or other chemicals but, in humans, the chronic ingestion of alcoholic beverages is the single most important cause. Histologically, cirrhosis is characterized by the presence of septae of collagen distributed throughout the major portion of the liver (19). The pattern of hepatic blood flow is invariably altered and, in most cases, single-cell necrosis is a major element in its pathogenesis. The necrotic process is associated with a deficiency in the repair mechanism of the residual cells, leading to fibroblastic activity and scar formation. The pathogenesis of cirrhosis is not well understood.

Lipid peroxidation has been hypothesized as the mechanism of liver injury induced by certain chemicals, particularly carbon tetrachloride. According to Recknagel and Ghoshal (20), free radicals arising from the homolytic cleavage of carbon tetrachloride attack the methylene bridges of

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unsaturated fatty acid side chains of microsomal lipids, resulting in morpho-
logic alteration of the endoplasmic reticulum, loss of drug-metabolizing
enzymatic activity, loss of glucose-6-phosphatase activity, loss of protein
synthesis and loss of the capacity of the liver to form and excrete low-
density lipoprotein. The investigators showed that conjugated dienes, typical
of peroxidized polyenoic fatty acids, occurred in animals and in man subjected
to intoxicating doses of carbon tetrachloride. These studies, together with
extensive investigations carried out by Recknagel and his co-workers (21),
have been the foundation of the lipid peroxidation theory as it concerns
carbon tetrachloride liver injury. Lipid peroxidation has also been reported
in animals after administration of other chemicals, including chloroform,
tetrachloroethane, iodoform and phosphorus (10). However, the role of lipid
peroxidation as the mechanism for necrogenic hepatic effects induced by these
chemicals has not been established and is at present controversial.

A wide variety of chemicals has been shown to induce hepato-
carcinogenic changes in laboratory animals (7, 22). These include some dial-
kylnitrosamines, some organochlorine pesticides, certain polychlorinated
biphenyls, carbon tetrachloride, chloroform, vinyl chloride, urethane and
others. However, in humans, there is no direct evidence that establishes any
chemical agent as the causative factor for liver cancer, with the exception of
vinyl chloride (22). The evidence for the other chemicals in humans appears
to be largely indirect, the result of extrapolation or conclusions drawn on
the basis of limited epidemiological studies. There is increasing evidence
that chemical hepatocarcinogens do not induce cancer but rather initate a
chain of events that results in cancer (23). Farber (23) has proposed that
the histogenesis of hepatocellular carcinoma involves a series of at least
four altered or new hepatocytic populations that evolve into malignant neo-
plasia, with each population developing from its immediate precursor by a
process of selection. An alternative theory is that each new cell population
is derived from the target cell, rather than the precursor population, and is
independent and unrelated to the others. Neither of these two hypotheses has
been validated.

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II.2.5   Nephrotoxicants

Chemicals in the occupational environment which have the capability to cause injury to the kidney comprise a group of major toxicological significance. The primary function of the kidney is the excretion of waste but this organ also has a significant role in the regulation of total body homeostasis (24). The kidney is the predominant organ involved in regulation of extracellular volume and in control of electrolyte and acid-base balance. In addition, this organ has an endocrine function and is the major site of formation of hormones that influence systemic metabolic functions (erythropoietin, renin-angiotensin-aldosterone, prostaglandins and kinins). Thus, the kidney is a metabolically and functionally active organ, any or all of whose functions can be affected by a toxic insult.

A brief review of the anatomy and physiology of the kidney may be helpful in understanding the effects of toxicants on the kidney. Anatomically, the two major areas of the kidney are the cortex and the medulla, with the cortex constituting the major portion and receiving most of the blood flow to the organ. Thus, the cortex will receive a greater fraction of chemicals in the blood than the medulla. The functional unit of the kidney is the nephron, which may be considered in three portions: 1) the vascular element, including the afferent and afferent arterioles; 2) the glomerulus; and 3) the tubular element. The vascular element serves to deliver waste and other materials to the tubule for excretion, return reabsorbed and synthesized materials to the systemic circulation and deliver oxygen and metabolic substrates to the nephron. The glomerulus, which is a specially developed and relatively porous capillary, acts as a selective filter of the plasma. Depending on their molecular size and net charge, certain materials will be filtered by the glomerulus into the lumen of the tubule while others will not be filtered and will remain in the circulation. The tubular element selectively reabsorbs the bulk of the filtrate (salt, water, filtered sugars, amino acids) and selectively eliminates waste materials. Also, the tubular element, particularly the proximal tubule, actively secretes material into the urine. This secretory activity is responsible for most of the excretion of certain compounds and for the elimination of hydrogen and potassium ions.

There are four reasons why the kidney is highly susceptible to foreign chemicals. First, the kidney has a much greater blood supply than many other organs with the result that a large fraction of any circulating toxicant will rapidly reach the kidney. A second functional property of this organ that contributes to the frequency of renal toxic effects is the ability of the kidney to extract substances from the blood and to accumulate them within the renal parenchyma or in the tubular lumen. An example of this effect is the renal secretion of organic acids, leading to high intracellular concentrations of certain substances such as para-aminohippurate (PAH). A third aspect of renal function that contributes to the frequency of toxic effects in the kidney is the fact that filtered substances may be concentrated in the tubular lumen as a result of salt and water reabsorption. As salt and water are reabsorbed from the glomerular filtrate, the materials remaining (including the potential toxicant) in the urine may be concentrated in the tubule. Thus, a nontoxic concentration of a chemical in the plasma could become toxic in the kidney subsequent to concentration within the kidney. Besides high intratubular concentrations of certain solutes, significant interstitial accumulation may also result from the countercurrent concentrating mechanisms in the renal medulla. The countercurrent exchange of small molecules is responsible for the considerable osmolar gradients required to concentrate urine and could lead to higher levels of diffusible and potentially toxic molecules such as cyanide or fluoride in the renal medulla than in other tissues. Thus, foreign chemicals may become especially toxic to the kidney because of normal renal mechanisms leading to high intraluminal, intracellular and interstitial concentrations of the compounds.

The fourth reason for the unusual susceptiblity of the kidney to toxicants is that normal tubular functions permit toxic interactions in the kidney that cannot readily occur in other organs. An example of this phenomenon is the normal secretion of hydrogen ions in the nephron for maintenance of normal acid-base balance and correction of metabolic acidosis. Chemicals, such as sulfonamides, whose solubility changes with pH may precipitate in the acidified tubular fluid and block the normal flow of urine. Alternatively, a toxic effect may be produced by a chemial species that is set free from an inactive precursor by the action of hydrogen loss. This mechanism may be responsible for the toxicity of uranyl ion circulating in plasma as a relatively inert but acid-labile complex (25).

The most common nephrotoxic chemicals include the heavy metals (mercury, chromium, cadmium, lead) and their compounds, certain halogenated hydrocarbons, a variety of agricultural and industrial chemicals and some analgesic, anesthetic and antibiotic drugs (24). Most heavy metals are potent nephrotoxic agents, with relatively low doses producing glucosuria, aminoaciduria and polyuria. Higher doses result in renal necrosis, anuria, increased BUN and death. These chemicals are believed to produce their nephrotoxicity by a similar mechanism, involving necrosis of the proximal tubules. It has been postulated that the tissue destruction could lead to sloughing of proximal tubular cells into the lumen and consequent tubular occlusion. The occlusion could be of sufficient magnitude to increase intratubular pressure and thereby decrease the glomerular filtration rate. However, this hypothesis is not supported by the results of some investigators who believe that the nephrotoxicity of heavy metals is at least partially due to a vasoconstrictive effect (26). It is probable that the nephrotoxicity of these chemicals results from a combination of ischemia secondary to vasoconstriction and their direct cellular necrotic effects.

Mercury and chromium, and their compounds, have been the most widely studied nephrotoxic heavy metals. Mercury may be introduced in the body as elemental mercury, as inorganic mercury or in organic form (24). Most recently, the environmental pollutant, methylmercuric chloride, has been found to produce renal damage in man and animals. The basic biochemical mechanism whereby mercury produces cellular damage in the kidney has not been established. However, the ability of this metal to combine with sulfydryl groups and inhibit a variety of enzyme systems has been well demonstrated. Chromium compounds, in sublethal doses, produce a proximal tubular necrosis that is similar to that produced by mercury except for its location in the proximal convoluted tubule instead of the pars recta. In addition to mercury and chromium, other metals have been reported to produce renal damage in animals or man. These include uranium, lead, cadmium, arsenic, gold, iron, antimony, platinum and thallium.

Several halogenated hydrocarbons have also been shown to be nephrotoxic. Of these, chloroform and carbon tetrachloride have been the most widely studied. With both of these chemicals, the functional lesion in the kidney appears to be primarily due to proximal tubular damage, although structural alterations have been found in other portions of the nephron as well. Functional changes produced by these chemicals include polyuria, glucosuria and proteinuria at low doses, with anuria and complete renal failure at higher doses. There is considerable evidence that the nephrotoxic effects of chloroform and carbon tetrachloride are due to an active metabolite of these chemicals. Other halogenated hydrocarbons such as bromobenzene, trichloroethylene and trichloroethane have also been reported to be toxic to the kidney and to cause effects similar to those of chloroform and carbon tetrachloride.

Various pesticides, herbicides and industrial chemicals may also produce effects on the kidney. Examples of these chemicals include 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T), paraquat, polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), and tetrachlorodibenzo-p-dioxin (TCDD). Although these compounds do not all have direct nephrotoxic action, they are all capable of influencing renal function. Some of these chemicals (PCBs, PBBs, TCDD) are capable of stimulating the drug-metabolizing enzymes in the kidney.

Nephrotoxic effects have also been reported in animals or man following the administration of a variety of drug substances, including analgesics, anesthetics and antibiotics. Large doses of these drugs over prolonged periods of time are generally required to produce these effects. Examples of drugs associated with nephrotoxicity include phenacetin, aspirin, methoxyflurane, streptomycin, neomycin and certain tetracyclines. In man, penicillins and sulfonamides have been implicated in an inflammatory interstitial nephritis but this appears to be due to an immunologic-type mechanism.

II.2.6   Cardiotoxicants

Certain industrial chemicals have the capability to produce toxic effects on the heart and may be categorized as cardiotoxicants. Many of these agents, however, are also capable of causing serious toxic effects to

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other organs such as the central nervous system, liver or kidney. With some of these chemicals, their potential cardiac effects have generally received less attention than their effects on other organs.

The principal chemical group associated with cardiotoxic activity is the low molecular weight halogenated alkanes, particularly certain fluoroalkanes. Many of these chemicals are in industrial use as fire extinguishing agents, refrigerants and solvents. Some fluoroalkanes are widely used as aerosol propellants and one fluoroalkane, halothane, has been in common use as an anesthetic. Many of the compounds have a relatively high vapor pressure under ordinary conditions, so that they can attain toxicologically significant concentrations in the air. Exposure to toxic levels usually occurs by inhalation. Availability to the alveolar membrane, coupled with lipid solubility, results in a potential for quantitatively significant pulmonary absorption of these chemicals.

The most important toxic effects of the haloalkanes are on the central nervous system and cardiovascular systems. Although CNS effects may occur at lower concentrations, these chemicals can also produce clinically important cardiovascular effects, such as cardiac arrhythmias and changes in cardiovascular dynamics, which may constitute a life-threatening hazard. The occurrence of cardiac arrhythmia as a result of interaction of a halogenated hydrocarbon with a pressor amine was observed with chloroform and epinephrine more than 80 years ago. Since then, the concept was proposed that halogenated hydrocarbons can "sensitize" the heart to the arrhythmogenic action of epinephrine, norepinephrine and other pressor amines. This sensitization action has been demonstrated for a large number of aerosol propellants, fire extinguishing agents and refrigerants, including trifluorobromomethane (Halon 1301®) bromochlorodifluoromethane (Halon 1211®), dichlorodifluoromethane (Freon 12®), methylene chloride, tetrachloroethylene, trichlorotrifluoroethane and trichloroethylene (27, 28). Additionally, nonhalogenated hydrocarbons such as hexane, heptane, xylene and toluene have been reported to sensitize the heart to epinephrine in experimental animals (29).

The concern for the interaction between these chemicals and amines is based on the supposed release of endogenous epinephrine from the

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adrenal medulla during excitement, fear or other stressful stimuli. Under stress, not only is epinephrine liberated from the adrenal medulla but also adrenergic transmitter (probably norepinephrine) is elaborated at the adrenergic terminals of the sympathetic innervations of the heart. It is possible that cardiac sensitization was the underlying mechanism in a number of sudden unexplained deaths associated with the sniffing of glue, solvents and gasoline or with industrial over-exposure to benzene and trichloroethylene (28).

The second major cardiotoxic effect of the haloalkanes is depression of myocardial contractility, which reduces cardiac output and lowers systemic arterial blood pressure. This effect has been demonstrated in animals following administration of a number of fluorinated propellants and chlorinated solvents (27, 28). Of the latter compounds investigated, trichloroethylene was found to have the most potent hemodynamic effects. Although the exact mechanisms of the effects of these haloalkanes on myocardial contractility are not known, disturbances of myocardial energy metabolism have been observed (27).

II.2.7   Carcinogens

The group of chemicals designated "chemical carcinogens" includes those chemicals which induce carcinomas, i.e., epithelial malignancies. In general usage, however, even chemicals that give rise to benign tumors are considered carcinogens since even this type of tumor is evidence of carcinogenicity (30). Historically, soot and coal tars were the first substances identified as carcinogenic when, in the late eighteenth century, a high incidence of scrotal cancer was found in chimney sweeps. Since then, a highly diverse collection of chemicals has been included in the category of carcinogens. This collection includes drugs, metals, laboratory chemicals and occupational chemicals, i.e., chemicals to which workers may be exposed in an occupational environment.

Occupational carcinogens are identified by two main types of evidence: 1) epidemiologic studies or surveys of industrial operations where both environmental and medical data are available, and 2) experimental animal studies, encompassing long-term or life-term bioassays (31). The designation

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of a particular chemical as a "human" carcinogen or a "suspect" carcinogen by the ACGIH and governmental agencies is based on the type of evidence. Human carcinogens are recognized to have carcinogenic potential in man as a result of extensive epidemiological studies or industrial surveys of workers under conditions of actual exposure. Suspect carcinogens are chemicals which are suspect of inducing cancer in man on the basis of results of animal studies or from limited epidemiological evidence. The differentiation between human and suspect carcinogens is discussed in greater detail in subsequent sections. However, the reader should be aware that many of the chemicals mentioned in this section are suspect carcinogens for which conclusive epidemiological evidence of their carcinogenic potential in man has not been established.

Chemical carcinogens have been classified by some investigators according to their mechanism of action. A mechanistic classification of carcinogenic chemicals into eight classes, as proposed by Weisburger and Williams, is shown in Table II-3 (30). These classes are divided into two general categories, i.e., genotoxic and epigenetic. The genotoxic category which is comprised of carcinogens that interact and alter cellular DNA contains organic chemicals that are electrophilic reactants either in their parent form or after metabolism. The category of epigenetic carcinogens contains the five classes of carcinogens for which there is presently no evidence of genotoxicity (interaction with DNA). Possible mechanisms of action of members of this category may involve chronic tissue injury, hormonal imbalance, immunological effects, promotional activity on cells that have been altered or interaction with protein or RNA leading to faulty cellular differentiation (30, 32).

In the genotoxic category, there are three classes of chemical carcinogens. The direct-acting or primary carcinogens are comprised of a variety of organic chemicals, many of which are potential contaminants of the occupational environment. These chemicals include alkyl imines, alkylene epoxides, aryl epoxides, small-ring lactones, sulfate esters, mustards, active halogen compounds and nitrosamides. In the active halogen group, bis(chloromethyl)ether has been reported to cause cancer of the upper respiratory tract of humans exposed to apparently low levels of this chemical (33). Ethylene dibromide and dibromochloro-propane, which are utilized extensively in the

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TABLE II-3. CLASSES OF CARCINOGENIC CHEMICALS (30)

TYPE	MODE OF ACTION	EXAMPLE
A. Genotoxic		
1. Direct-acting or primary carcinogen	Electrophile, organic compound, genotoxic, interacts with DNA	Ethylene imine, bis(chloromethyl)ether
2. Procarcinogen or secondary carcinogen	Requires conversion through metabolic activation by host or *in vitro* to type 1	Vinyl chloride, benzo(a)pyrene, 2-naphthylamine dimethylnitrosamine
3. Inorganic carcinogen	Not directly genotoxic, leads to changes in DNA by selective alteration in fidelity of DNA replication	Nickel, chromium
B. Epigenetic		
4. Solid-state carcinogen	Exact mechanism unknown; usually affects only mesenchymal cells and tissues; physical form vital	Polymer or metal foils, asbestos
5. Hormone	Usually not genotoxic; mainly alters endocrine system balance and differentiation; often acts as promoter	Estradiol, diethylstilbestrol
6. Immunosuppressor	Usually not genotoxic; mainly stimulates "virally induced," transplanted, or metastic neoplasms	Azathioprine, antilymphocytic serum
7. Cocarcinogen	Not genotoxic or carcinogenic, but enhances effect of type 1 or type 2 agent when given at the same time. May modify conversion of type 2 to type 1	Phorbol esters, pyrene, catechol, ethanol, n-dodecane, SO$_2$
8. Promoter	Not genotoxic or carcinogenic, but enhances effect of type 1 or type 2 agent when given subsequently	Phorbol esters, phenol, anthralin, bile acids, tryptophan metabolites, saccharin

chemical industry and in agricultural practice, induce tumors quickly and in large numbers and are considered powerful carcinogens (30).

The second genotoxic class, the procarcinogens or secondary carcinogens, contains most of the known chemical carcinogens. These chemicals require conversion by biochemical metabolic activation into direct-acting carcinogens to produce their carcinogenic activity. The procarcinogen class includes several types of chemicals, including the polynuclear aromatic hydrocarbons (PAHs), certain aromatic amines, alkylnitrosamines and related compounds, mycotoxins such as aflatoxin B$_1$, pyrrolizidine alkaloids, certain plant toxins and others. Of these chemical groups, the polycyclic or hetereocyclic aromatic hydrocarbons have been the most extensively studied chemical carcinogens, particularly in the area of structure-activity relationships

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(30). These studies have shown that many PAHs that are carcinogenic are derived from a benz(a)anthracene skeleton. Addition or substitution of certain groups in the skeleton can yield chemicals with powerful carcinogenic activity, such as benzo(a)pyrene and dimethylbenz(a)anthracene which is one of the most potent synthetic PAH carcinogens known.

Other important procarcinogens are certain aromatic amines and other nitrogen-containing chemicals. In the first reports of bladder cancer in men exposed to aromatic amines, these cancers were labeled "aniline" cancers because the workman were exposed to a variety of aniline derivatives in dyestuff manufacture (34). Currently, animal studies suggest that a number of substituted anilines, particularly where the substitution is by an ortho-methyl group, may be carcinogenic. Some examples of carcinogenic aromatic amines are o-toluidine, benzidine, 2,4,6-trimethylaniline, toluene-2,4-diamine, 2-naphthylamine and 2-anthramine. In addition to these aromatic amines, many other nitrogen-containing organics, including certain nitrosamines, nitrosamides, azo dyes, dialkylhydrazines and thioamides, have been found to have carcinogenic activity.

Miscellaneous organic chemicals which are sometimes included as genotoxic procarcinogens are dioxane, benzene, chloroform, ethylene bromide, vinyl chloride, carbon tetrachloride and ethyl carbamate. Evidence that these chemicals are genotoxic, or, even procarcinogens, is not definitive in all cases.

The third class of genotoxic carcinogens is the inorganic carcinogens. Compounds of uranium, polonium and radium have carcinogenic activity which is attributed chiefly to their radioactive properties. Uranium, radium and radon gas have been implicated in the development of lung cancer in individuals engaged in mining ores. A higher incidence of this cancer has been found in miners who smoke cigarettes, indicating a possible synergistic effect between ore dust, radiation and cigarette smoking (35). Other inorganic chemicals, including titanium, nickel, chromium, cobalt, lead, manganese and beryllium, and certain of their derivatives, have been found to be carcinogenic under specific experimental conditions. Among these, salts of nickel and titanium appear to be the most potent, leading to cancer formation

usually at the point of application of the chemical in animals. Arsenic has also been reported to be carcinogenic, with an apparent association between trivalent inorganic arsenic exposure of humans through drinking water or certain occupations and the development of lung and skin cancer and lymphomas (30).

The epigenetic carcinogen category includes chemicals and drugs which, in many cases, are not encountered in the occupational environment. The five classes in this category, with examples, are: 1) solid-state carcinogens (polymer or metal foils, asbestos); 2) hormones (estradiol, diethylstilbestrol); 3) immunosuppressors (antilymphocytic serum); 4) cocarcinogens (phorbol esters, pyrene, ethanol, n-dodecane, SO_2); and 5) promoters (phorbol esters, phenol, anthralin). Occupational exposures to members of the latter two classes of chemicals are more likely than to the former three. Cocarcinogens are agents that enhance the carcinogenic process caused by a genotoxic carcinogen when administered together with the carcinogen. Possible mechanisms of this enhancement include interference with the metabolism of the genotoxic carcinogen or an increase in the growth of cells with an altered genotype reflecting neoplastic change. Although the cocarcinogens do not, by themselves, cause cancer, they have practical importance by modifying the risk of cancer induced by the genotoxic carcinogens. For example, although tobacco smoke contains relatively small amounts of genotoxic carcinogens (PAHs, nitrosamines), cocarcinogens, such as catechol and other phenolic compounds, are also present. These carcinogenic factors are believed to play an important role in the overall effect of the smoke in the development of cancer in man (36).

Promotors are agents that increase the tumorigenic response to genotoxic carcinogens when administered after the carcinogen. Promotion, which is an epigenetic phenomenon, is highly dose dependent, requires the presence of the agent for a long time and is reversible. The mechanism of promotion has not yet been established. However, the discovery of this phenomenon with croton oil in experimental animals gave rise to the "two-stage" concept of carcinogenesis, initiation and promotion. According to this concept, a tissue or organ appropriately altered by exposure to a carcinogen (initiation phase) is encouraged by a promoter to develop a malignant neoplasm

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(promotion phase). Promotion may be effective even if it occurs a long time after the initiating event. Thus, application of phorbol esters from crotol oil several months and, even one year, after application of PAH to mouse skin resulted in the production of skin tumors (37).

The proposed distinction between genotoxic and epigenetic carcinogens, if validated, is important to both human risk assessment and to regulatory actions to ensure safety (30). Genotoxic chemicals, because of their effects on genetic material, pose a definite qualitative hazard to humans. These chemicals are occasionally effective after a single exposure, produce cumulative effects and act together with other genotoxic carcinogens having the same target organ. Thus, the level of human exposure acceptable for "no risk" is difficult to establish and zero exposure is often the goal, particularly with powerful carcinogens of this category. In contrast, with some classes of epigenetic carcinogens, carcinogenic effects occur only after high and sustained levels of exposure that cause prolonged physiologic abnormalities, hormonal imbalances or tissue injury. Consequently, the risk from exposure to these agents may be quantitative in nature and it may be possible to establish a "safe" threshold of exposure for these chemicals.

II.2.8   Hematopoietictoxicants

Although the respiratory and nervous sytems, the liver and kidney are the principal target sites, virtually every organ or system in the body may be affected by the vast number of potential toxicants in the occupational environment. One of the most important organs or systems that may be affected by marine chemicals is the formed elements of the blood because of the serious consequences that may result from their injury. Drugs or chemicals which produce effects on the formed elements of the blood are designated hematopoietictoxicants. Examples of these toxicants and their effects have been reviewed by Smith (38).

The formed elements of the blood include the rea cells (erythrocytes), platelets (thrombocytes) and several types of white cells (leukocytes). The red cell and its hemoglobin perform the essential function of transporting oxygen from the lungs to the tissues of the body. The platelets

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of the blood function in the clotting or coagulation of blood. When chemicals cause damage to platelets or a reduction in their number, hemorrhagic disorders may result. The primary function of the leukocyte system (lymphocytes, monocytes, neutrophils, eosinophils, basophils) is the defense of the body against foreign organisms or extraneous materials by two primary mechanisms. These are phagocytosis and antibody production.

Foreign chemicals may affect the formed elements of the blood by actions on their production in the bone marrow, by increasing their rate of destruction in the peripheral blood or by altering their distribution in the various body compartments (38). Anemia can result if the rate of red cell destruction exceeds the normal rate of production. Examples of chemicals which can cause anemia by hemolytic action are phenylhydrazine, arsine and naphthalene. Other chemicals can cause severe damage to the bone marrow, with a resultant decrease in formation of all three major groups of formed elements (pancytopenia). Examples of chemicals and drugs associated with this condition are benzene, mustard gas, arsenic, trinitrotoluene, hydantoin derivatives and phenylbutazone.

Acute damage to the red cell or reduction in the number or hemoglobin content of these cells can impair oxygen transport and cause a hypoxic condition in the tissues. Hypoxia characterized by a lowered oxygen capacity when the arterial PO_2 and rate of blood flow are normal or elevated has been termed anemic hypoxia. The most common example of a chemical that causes this type of hypoxia is carbon monoxide. This gas reversibly combines with the hemoglobin of the red blood cell, thereby limiting its capacity to carry oxygen, and impairs the transport of oxygen to tissues. In such cases, the signs and symptoms are due secondarily to damage to the CNS and/or, heart which are particularly senstive to a low oxygen supply. Other chemicals, including sodium nitrite, aniline, nitrobenzene, can cause anemic hypoxia by another mechanism, the conversion of hemoglobin to methemoglobin. The heme iron of hemoglobin is susceptible to chemical oxidation involving a valence change from the ferrous to the ferric state. When this oxidation occurs, the resulting greenish brown to black pigment, methemoglobin, can no longer combine reversibly with oxygen or with carbon monoxide.

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Another form of hypoxia, histotoxic hypoxia, refers to a condition in which the peripheral tissue PO_2 is often normal or even greater than normal, but the cells are unable to utilize oxygen. Two chemicals are thought to act by this mechanism, hydrogen sulfide and hydrogen cyanide. Hydrogen cyanide interrupts electron transport in the cytochrome chain by inhibiting cytochrome oxidase, thereby compromising oxidative metabolism and phosphorylation. Hydrogen sulfide is also an inhibitor of cytochrome oxidase and, in animals, produces symptoms similar in almost all respects to those produced by cyanide. The only notable exceptions are conjunctivitis and occasionally pulmonary edema produced by chronic exposure to low concentrations of hydrogen sulfide.

A third form of hypoxia, anoxia hypoxia, is characterized by a lower-than-normal PO_2 in arterial blood when the oxygen capacity and rate of blood flow are normal or elevated. This condition results from exposure to sensory irritants or drugs that depress the respiration. Examples of common industrial chemicals capable of producing sensory irritation with subsequent anoxia hypoxia are ammonia, hydrogen chloride and sulfur dioxide.

II.2.9   Sensitizing Agents

A sensitizing agent is defined by Loomis (39) as a chemical that produces a sensitization (allergic) reaction in an individual or, in other words, a response involving an immume mechanism. The term "sensitization reaction" has frequently been used incorrectly to refer to the response of "hypersensitivity." The latter response does not involve the immune system or require preconditioning of the individual to the chemical and is considered a normal pharmacologic or toxicologic response of greater intensity than that which occurs in the majority of the population. In contrast, a sensitization or allergic reaction is an abnormal effect of the chemical in the sense that it differs from the toxicologic effect that results from excessive doses of the chemical. Because the magnitude of an allergic reaction is usually not dose-related in the typical sigmoid dose-response manner characteristic of most toxic effects, these reactions have not been considered by some to be a toxic response (40). However, these responses, which often are very severe and may be fatal, do meet the definition of toxicity as an adverse effect on living organisms.

The subject of sensitization reactions as a toxic response was reviewed in detail by Loomis (39). Sensitization requires preconditioning of the individual to a chemical and involvement of an immune mechanism. The immune mechanism involves the following events: The initial exposure to a chemical substance, an induction period and finally the production of a new protein called an antibody. As illustrated in Figure II-1, the compound or metabolic product of the chemical acts as a haptene, combining with an endogenous protein to form an antigen. An antigen is capable of eliciting the formation of cellular or humoral new proteins called antibodies. Thus, the initial exposure results in the formation of antibodies and "sensitization" to subsequent expsoures to the chemical but does not cause cellular damage. The induction of the formation of antibodies by the antigen is referred to as the "sensitizing" part of the immune mechanism. On a subsequent exposure, the chemical or its metabolic product again reacts with endogenous protein to form

INITIAL EXPOSURE	SUBSEQUENT EXPOSURE
Compound or its metabolic product (HAPTENE)	Compound or its metabolic product (HAPTENE)
↓	↓
Conjugation with protein (ANTIGEN)	Conjugation with protein (ANTIGEN)
↓	↓
Antigen elicits formation of cellular or humoral proteins (ANTIBODIES) ⟶	ANTIGEN-ANTIBODY REACTION
	↓
	Cellular damage
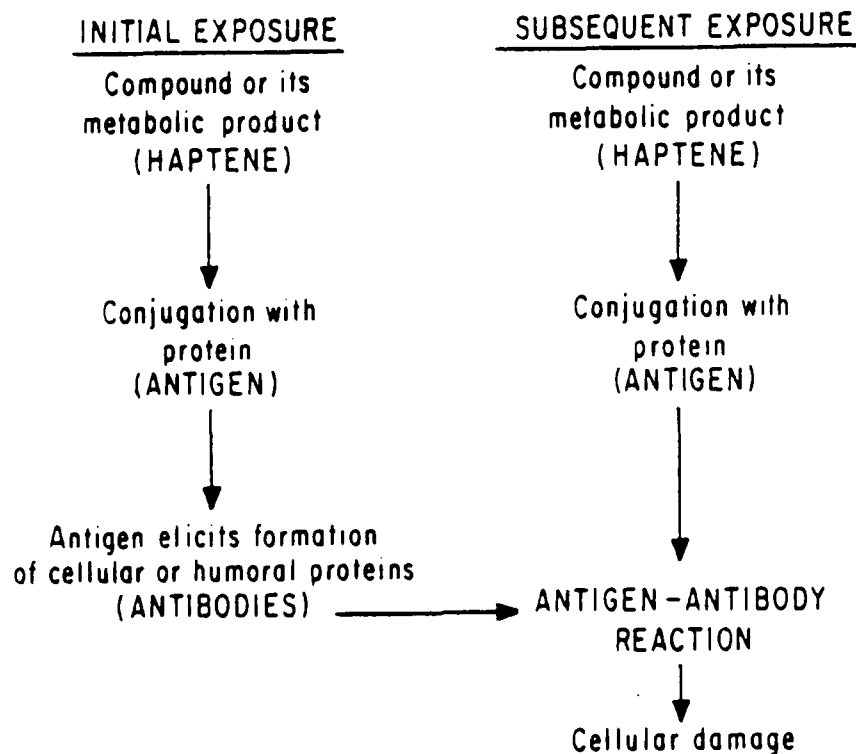
FIGURE II-1. THE ALLERGENIC MECHANISM OF SENSITIZATION
RESPONSES TO CHEMICALS (39)

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an antigen, which reacts with the preformed antibodies and leads to a response in the tissues in the form of cellular damage. This response consitutes the reaction part of the immune mechanism and is commonly referred to as the "allergic response," "immune response" or "sensitization reaction."

The fact that simple chemicals can initiate the immune response was first demonstrated by Landsteiner and co-workers approximately 40 years ago (39). These investigators showed that doses of certain dinitrobenzene derivatives could be injected or applied without producing toxic effects in animals but that subsequent (7-14 days later) administration of the same or a closely related chemical would induce a tissue response at the site of application or systemically. Landsteiner's theory that the halogen in these derivatives resulted in binding of the chemical with endogenous protein carrier and that this complex elicited formation of antibodies became commonly known as the "hapten theory" of antibody formation. Since his work, considerable knowlege of haptens, immune responses and the mechanisms of these responses has evolved. Based on the type of chemical inducing such responses, two types of immune responses have been differentiated. The first type results from naturally occurring large molecules such as proteins or lipids. The second type, which is important in the industrial environment, is produced by simple compounds, most of which are small molecules. Similar mechanisms are involved in both types of immune response. However, the simple chemicals make up the majority of the chemicals of toxicological interest.

Many simple chemicals have haptenic potential; however, they differ widely in their degree of such activity. Phenol, for example, is rarely antigenic whereas the drug, phenylethylhydantoin, induces allergic symptoms in virtually every human who receives the drug on multiple occasions (41). The conferring of haptenic properties on a chemical appears to depend on certain chemical groupings. In a similar manner, the formation of the hapten-protein complex is dependent on the presence of certain radicals on specific amino acids of the endogenous protein. A number of chemical groupings on the hapten and on the protein which would be expected to lead to formation of the complex is shown in Table II-4. The hapten-protein complex involves a firm binding mechanism which has been attributed to a covalent bonding that causes the loss of the chemical characteristics of both the

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TABLE II-4. SOME REACTIVE GROUPS ON HAPTENS AND ON AMINO ACIDS WHICH ARE
CAPABLE OF REACTING IN THE FORMATION OF ANTIGENS (39)

ON HAPTEN		ON AMINO ACID	
Diazonium	$-N = N^+$	Serine	$-OH$
Thiol	$-SF$	Lysine	$-NH_2$
Sulfonic Acid	$-SO_3H$	Arginine	$-NHC-NH_2$
Aldehyde	$-CHO$		NH
Quinone	$O = \langle \rangle = O$	Cysteine	$-SH$
Active Halogen		Cystine	$-S-S-$
		Tyrosine	$--\langle \rangle-OH$

hapten and the protein. Chemicals that combine with protein in a readily
reversible manner, such as by ionic binding or by Van der Waal's forces proba-
bly do not form antigens. Many chemicals have been found to be sensitizers
(haptens) in the intact animal but do not appear to react with protein in
vitro. Such chemicals are believed to undergo metabolic alteration in vivo,
yielding products that act as haptens.

The formation of antibodies is induced by reaction of the
antigen with cells of the lymphoid tissue of the body. The antibodies (immune
globulin) appear in the circulating plasma in certain globulin fractions of
the plasma proteins and may be detected by various serologic methods. Their
appearance in the plasma occurs after a latent period following initial admin-
istration of the hapten. This is followed in succession by a log phase period
of exponential rise in the antibody concentration (titre) of the blood, a
secondary stationary phase of constant antibody concentration and a subsequent
decay period in antibody concentration. Whether administration of a challeng-
ing dose of a sensitizing agent elicits an immune response depends on the time
of the administration and the level of the antibody titre at that time. If
administration occurs at a time when the antibody concentration is high, the
immune response would be expected to be more extensive than when the titre was
low.

The antigen-antibody reaction causing the immune response probably involves a weak bonding mechanism using ionic or Van der Waal's forces. When the antigen is a complex chemical, the reaction is frequently highly specific, i.e., only the specific antigen or hapten that was used for sensitization reacts with the antibody; however, when the hapten is a simple chemical, the antigen-antibody reaction is not always entirely specfic for the hapten. The term "cross-sensitization" is used to indicate that an induced antibody may react with antigens formed from haptens of similar chemical structures. This phenomenon is of considerable importance in immune reactions to certain foreign chemicals with similar structure such as the o-, m- and p-isomers of hydroxybenzoic acid. The extensive use of the esters of these chemicals as preservatives in nutrients, cosmetics, soaps and drug preparations has resulted in cross-sensitization reactions. The phenomenon is of particular importance to drugs because many series of drugs have been developed, such as the barbiturates, the synthetic narcotics and the sulfonamides, in which members of a series have similar pharmacologic actions, are of similar structure and are similarly biotransformed in the body. Thus, sensitization may result from administration of one member of a series but the immune response may occur with subsequent administration of any of several other members of the series of drugs.

The antigen-antibody response may occur locally or systemically and may be immediate or delayed following administration of the challenging dose of the hapten. The immediate type of reaction occurs within a few minutes, or at most a few hours, after the challenging dose and is probably the result of the liberation of histamine from its storage sites within the body. Evidence for the role of histamine has been obtained from observation of a remarkable degree of uniformity between the pharmacologic response induced by the administration of histamine and the response induced by allergic mechanisms in various species of animals. In man, the response is manifested as an anaphylactic reaction, as serum sickness, as an atopic effect on the skin or mucous membranes, or as hay fever and asthma.

The delayed antigen-antibody response may not occur for a period of one to several days after the challenging dose of the chemical. This type of response is probably not related to the liberation of histamine,

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but represents a direct destructive action on certain specific cells or tissues as a result of the antigen-antibody reaction. The delayed responses may be systemically manifested as blood dyscrasias and as specific organ damage, or frequently are manifested locally as a wide range of dermatologic effects.

Gell and Coombs (42) have classified allergic reactions into four types. The first is the anaphylactic type, which may be general or local and may involve the skin (urticaria), the respiratory tract (asthma) or the gastrointestinal tract (food allergy). The second type of allergic reaction is cytolytic or cytotoxic and is manifested as blood dyscrasias in which the antigen component involves one or more types of blood cells. In the third type, local edema and necrosis following subcutaneous injection of the antigen or serum sickness syndrome are typical effects. The fourth is a delayed reaction type manifested as a local irritation reaction.

Representative examples of the various types of allergic reactions that occur in humans and some examples of drugs involved are shown in Table II-5. It should be noted that the intensity and nature of these reactions vary from individual to individual and even in the same individual. Thus, on one occasion or in one person, the response may be manifested as a cutaneous reaction, in another it may be a vascular response, and in a third it may be a blood cell suppression response. Also, chemicals may be well tolerated by an individual for days, months or years and suddenly give rise to a sensitization reaction.

It is apparent from the table above that many drugs have been identified as capable of causing allergic reactions. In fact, much of our knowledge of sensitization has evolved from observations of human reactions following use of drugs and subsequent animal experimentation. In addition, many chemicals have been identified as sensitizing agents as a result of exposures of workers in the industrial and occupational environments. In a recent review by McGrath et al. (43), the authors stated that the expansion of industry and the rapid increase in the number of chemicals produced have led to the recognition of a number of relatively new allergic diseases. The magnitude of the problem of sensitization reactions to chemicals is evident from the report by the International Contact Dermatitis Research Group (ICDRG)

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TABLE II-5. SOME COMMON MANIFESTATIONS OF SENSITIVITY REACTIONS IN THE HUMAN
AND SOME COMMONLY ENCOUNTERED HAPTENS ASSOCIATED WITH THE SENSI-
TIVITY (39)

DERMATOLOGIC MANIFESTATIONS	CHEMICAL INVOLVED
Contact dermatitis (eczematoid reactions, itching, erythema, and vesiculation; later pustulation and necrosis)	Arsenicals, local anesthetics, mercurials, penicillin, quinacrine, streptomycin, sulfonamides
Urticaria (localized discrete or confluent areas of edema)	Organ extracts, penicillin, pollen extracts, salicylates, serums
Exanthematic (redness, macular or papular discrete areas)	Barbiturates, sulfonamides, arsenicals, iodides
Exfoliative (loss of superficial skin layers, redness, swelling, blood cell infiltration)	Arsenicals, barbiturates, gold salts, mercurials, quinacrine
Bullous eruptions (discrete serous or sero-pustular areas)	Arsenicals, bromides, iodides
Erythema multiforme (multiple types of lesions, macules, papules, nodules)	Bromides, salicylates, sulfonamides
Fixed eruptions (localized areas of eruption which reappear at same site upon repeated ingestion of hapten)	Barbiturates, phenolphthalein

SYSTEMIC MANIFESTATIONS	CHEMICAL INVOLVED
Blood dyscrasias	
1. Granulocytopenia (depression of granulocytes)	Aminopyrine, arsenicals, gold salts, hydantoins, phenylbutazone, thiouracils
2. Thrombocytopenia (depression of platelets)	Arsenicals, quinine, sulfonamides
3. Aplastic anemia (depression of all blood cells)	Chloramphenicol, hydantoins, quinacrine, phenylbutazone, sulfonamides
Serum sickness (fever, skin lesions such as urticaria, joint pain and swelling; lymphadenopathy)	Serums, penicillin, streptomycin, sulfonamides, thiouracil
Anaphylactic shock (flushing, lightheadedness, fall in blood pressure, respiratory airway obstruction; systemically induced)	Iodides, local anesthetics, mercurials, organ extracts, penicillin, pollen extracts, serums, vaccines
Asthma (or bronchiolar obstruction)	Pollen extracts, salicylates, serums
Organ damage Hepatitis	Gold salts, hydantoins, Phenurone, sulfonamides
Periarteritis	Serums, hydantoins, iodides, mercurials, sulfonamides

that, in a study of 4,000 workers, occupational skin disease accounted for 19.1 percent of absences from work. It has been estimated that approximately 50 percent of occupational dermatitis cases are allergic reactions.

Cutaneous reactions, respiratory disease and systemic ill-nesses have been reported in individuals following exposure to industrial chemicals (43). An occupational dermatosis has been defined as a pathological

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condition of the skin for which occupational exposure can be shown to be a major causal or contributory factor (44). This condition may be an allergic (sensitization) dermatitis or an irritant (toxic) dermatitis. Although each type of dermatitis accounts overall for about half the cases of occupational dermatoses, the incidence of each type varies considerably with the industry and the specific chemicals involved in the industrial environment. In some cases, the dermatitis is both irritant and allergic because damage to the skin from either form of dermatitis enhances penetration of irritants and allergens. A list of industrial chemicals reported to cause allergic contact dermatitis in workers together with the uses of these chemicals is shown in Table II-6.

Allergic occupational asthma has become increasingly recognized as a source of illness and absenteeism among industrial workers (45). However, the actual prevalence of this reaction is difficult to determine because it varies widely among countries and industries, with the causal agent and according to the number of workers exposed. It has been estimated that about 2 percent of all cases of asthma are occupational but, in Japan, some 15 percent of asthma in adult males is believed to be occupational (46, 47). In recent years there has been a steady increase in the number of potential asthma provoking agents in industry and this increase is predicted to continue into the future (43). There are several features that suggest that asthma is an allergic reaction (45). First, an attack does not occur upon initial exposure, indicating that a first exposure is necessary to produce sensitization. Second, usually only a proportion of the exposed workers are affected and the incidence is generally low. Third, the sensitivity to the causative substance increases with time and the reaction becomes worse with increased exposures. Finally, in clinical testing, the reaction can be elicited with low concentrations of the substance, often less than those generally encountered in the workplace.

Distinct patterns of asthmatic response have been identified in sensitized workers following controlled exposures in a hospital (47). An extensive list of substances reported to induce asthma and the pattern of response associated with each chemical are shown in Table II-7. The "immediate" pattern typically develops within minutes of exposure, is maximal at

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TABLE II-6. INDUSTRIAL CHEMICALS INDUCING ALLERGIC CONTACT DERMATITIS (43)

Sensitizing Chemical	Use
4-tertiary-Butyl catenol (TBC)	Antioxidant insoluble mineral seal oil
Phenolic calcium salt	Antioxidant lubricating oil
2-Mercaptobenzothiazole	Corrosion inhibitor soluble oil
Sodium mercaptobenzothiazole Grotan BK hexahydro-1,3,5-tris (2-hydroxyethyl) triazine	Antifreeze mixtures Bactericide, soluble oils
Chromates and Nickel Platinum	cutting fluids steel alloy antirust paints
Dyes-Azo and anthraquinone	antirust oil, gasoline, dyes
Ethylenediamine	Medical cream, stabilizer solvent
Methyloctylbenzenesulphonate	antistatic lubricant
Toluene diisocyanate (TDI)	polyurethane foam adhesives
Diphenylmethane diisocyanate (MDI)	polyurethane
Isophorone diisocyanate (IPDI)	polyurethane
Trimethyl hetamethaylene diisocyanate (TMDI)	paint
Triethylamine	polyurethane hardner
Triphenyl phosphate	plastics
Resorcinol monobenzoate	ultraviolet light absorber in plastics
Para-tertiary-butyl phenol	photo-oxidation and discoloration preventative in plastics
Ethylene glycol monomethyl ether acetate	plastic solvent
Turpentine	solvent

TABLE II-7. SUBSTANCES THAT INDUCE ASTHMA (43)

Sensitizing Agents	Types of Asthma*			Other Effects	Occupation
	Immediate	Late	Nonspecified		
METALS					
Boranes	+			Prolonged asthma	
Chromic acid		+		Dermatitis	Chrome plater
Potassium chromatic and dichromate		+			Chrome polisher
Potassium dichromate		+			Cement workers
Sodium bichromate		+			Chrome plater
Platinum salts	+	+		Rhinitis, conjunctivitis	Platinum refiners
Chloroplatinic acid		+		Nocturnal asthma	Platinum chemist
Nickel sulphate		+			Nickel plater
Nickel sulphate	+				Metal plating
Nickel carbonyl			+	Loffler's Syndrome	Chemist engineer
Vanadium and vanadium pentoxide			+		Gas turbine cleaners
Vanadium and vanadium pentoxide		+		Nocturnal asthma	Boiler cleaners
Cobalt	+				Tungsten grinder
Stainless steel (chromium & nickel)	+	+		Eczema	Welders

* + Indicates type of asthma reported in workers exposed to each substance in specific occupations.

TABLE II-7. SUBSTANCES THAT INDUCE ASTHMA (43)
(Continued)

Sensitizing Agents	Types of Asthma*			Other Effects	Occupation
	Immediate	Late	Nonspecified		
CHEMICALS					
Persulfate salts		+		Dermatitis rhinitis	Chemical workers
Fluorine		+			Aluminum pot room workers
Formalin	+				Match maker
Formalin			+		Laboraotry worker
Formalin		+			Phenolic resin moulder
Formalin	+	+		Recurrent asthma	Nurses
Tanic acid	+			Rhinitis, urticaria	Sunburn spray
Paraphenylene diamine	+	+			Fur dyers
Dimethyl ethanolamine	+	+			Paint sprayer
Aminoethyl ethanolamine	+	+			Aluminum cable soldering
Aminoethyl ethanolamine				Prolonged asthma	Aluminum cable soldering
Ethylene diamine	+	+			Rubber, shellac manufacturers; photography
Triethyl tetramine		+			Aircraft fitter
Chloramine T	+	+			Brewery workers

* + Indicates type of asthma reported in workers exposed to each substance in specific occupations.

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TABLE II-7. SUBSTANCES THAT INDUCE ASTHMA (43)
(Continued)

Sensitizing Agents	Types of Asthma*			Other Effects	Occupation
	Immediate	Late	Nonspecified		
CHEMICALS (Continued)					
Phthalic anhydride	+	+		Rhinitis	Paint manufacturer, tool setter, plastic moulder
Phthalic anhydride	+			Rhinitis	Plastics
Trimellitic anydride	+	+			Chair sprayer
Trimellitic anhydride	+	+		Systemic	Chemical workers
Trimellitic anhydride	+	+	+		Epoxy resins, plastics wire coatings
Colophony (pine resin)	+	+		Nocturnal asthma	Electronics manufacturer
Colophony (pine resin)	+				Electronics manufacturer, melt gluer
Polyether alcohol +polypropylene glycol	+				Solderer
Furan based, resin binder systems (furfuryl alcohol)		+		Rhinitis, lacrimation	Foundry mold maker
Polyvinyl chloride vapor (phthalic anhydride)	+	+		Increased by smoking	Meat wrappers (PVC softwrap)

* + Indicates type of asthma reported in workers exposed to each substance in specific occupations.

TABLE II-7. SUBSTANCES THAT INDUCE ASTHMA (43)
(Continued)

Sensitizing Agents	Types of Asthma*			Other Effects	Occupation
	Immediate	Late	Nonspecified		
CHEMICALS (Continued)					
Polyvinyl chloride vapour (phtalic anhydride)	+	+			Meat wrappers
Tetrachlorphthalic anhydride)	+	+		Severe systemic	Epoxy resin manufacturers
Himic anhydride	+				Ingredient in fire retardant materials
REACTIVE DYES					
Levafix brilliant yellow	+				Dye weighers
Drimaren brilliant yellow	+				Dye weighers
Drimaren brilliant blue	+				Dye weighers
Cibachrome brilliant scarlet	+				Dye weighers
Persulphate and henna	+	+			Hairdressers
ISOCYANATES					
Toluene diisocyanate (TDI)	+	+		Nocturnal asthma	TDI use
TDI	+	+			TDI manufacture
TDI	+				Office workers- source in neighboring factory
TDI	+	+		Nocturnal asthma	Plastics factory
TDI	+	+	+	Nocturnal fever	Foam manufacture
TDI					Tinners in elec- tronics industry

* + Indicates type of asthma reported in workers exposed to each substance in specific occupations.

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TABLE II-7. SUBSTANCES THAT INDUCE ASTHMA (43)
(Continued)

Sensitizing Agents	Types of Asthma*			Other Effects	Occupation
	Immediate	Late	Nonspecified		
ISOCYANATES (Continued)					
TDI			+		Foam manufacture
TDI	+	+		Nocturnal fever	Tinners in electronics industry
TDI	+	+			Foam manufacture
TDI	+	+		Nocturnal asthma	Toy maker
TDI	+	+			TDI manufacture
TDI	+	+			Boat builder, refrigerator manufacturer, printer laminators, tinners and insulators
TDI	+	+	+	Chronic lung disease	Foam and plastic manfacture
Hexamethylene diisocyanate (HDI)		+			Car sprayers paint testers
Diphenylmethane diisocyanate (MDI)	+	+			Laminators Printers
Diphenylmethane diisocyanate (MDI)				Hypersensitivity pneumonitis	Rigid foam insulators Foundry workers
Diphenylmethane diisocyanate (MDI)		+**			Polyurethane foam manufacture
Naphthalene diisocyanate (NDI)	+	+	+	Associated with smoking	Rubber workers Chemist

* + Indicates type of asthma reported in workers exposed to each substance in specific occupations.
** Indicates a possible effect.

approximately 10 to 20 minutes, subsides in a half to two hours and is characterized by wheeze and chest tightness. The "late" or "non-immediate" pattern usually starts several hours after exposure, is maximal at about 4 to 8 hours and subsides within 24 hours. The asthmatic response also may occur in the early hours of the morning with a tendency, in some cases, to recur the same time on a number of successive nights following a single exposure or challenge (recurrent late asthma). In this response, the wheeze is often slight or absent and, in some cases, the only symptoms may be cough, a small amount of sputum and mild breathlessness, but in others there may be influenza-like symptoms with fever. The third pattern, the "dual" or "combined" response is characterized by the occurrence of both the "immediate" and "late" patterns.

Of the many chemicals capable of inducing allergic asthmatic response, the isocyanates are used in the greatest variety of industries and result in sensitization of numerous workers in these industries (47). Toluene diisocyanate (TDI) is the most common isocyanate used commercially; other important isocyanates include hexamethylene diisocyanate (HDI), methylene diphenyl diisocyanate (MDI), naphthalene diisocyanate (NDI) and polymethylene polyphenyl isocyanate (PAPI). Occupations with potential risks of isocyanate exposure include diisocyanate workers, polyurethane foam makers, wire coating workers, plastic foam makers, plastic molders and rubber workers. It has been reported that 5 to 10 percent of isocyanate workers develop asthmatic symptoms, with some case reports of fatal status asthmaticus (48, 49). Vapors or aerosols, when inhaled, act as corrosive agents as well as allergens, causing irritant effects. The upper respiratory tract is primarily affected in experimental animals, with tracheitis, bronchitis and sloughing of the superficial epithelium occurring after 2 ppm for 4 hours. A variety of clinical manifestations have been reported in workers exposed to these chemicals, including, in addition to asthma, acute and chronic bronchitis, bronchopneumonia, bronchiectasis, bronchielitis obliterans, emphysema, hypersensitivity pneumonitis and pulmonary fibrosis. At the present time, there is considerable controversy over whether asthma induced by exposure to the diisocyanates is an immunologic response. Although many investigators believe that non-immunologic mechanisms are involved, recent convincing experimental evidence supports a possible role of immunologic factors in isocyanate-induced asthma (43).

II.2.10 Other Toxicants: Reproductive System Toxicants/Teratogens

In this section, two additional important classes of toxicants are reviewed, the reproductive system toxicants and the teratogens. These classes represent different types of toxicants even though the overall consequences of both are interference with the birth and development of healthy offspring. The two classes are differentiated by the definition of a reproductive system toxicant as a substance that causes an adverse effect on the reproductive system of either parent and of a teratogen as a substance that causes defects of fetal development. However, when a substance causes a defect in fetal development by interfering with the normal reproductive process, the agent is considered a reproductive system toxicant rather than a teratogen.

The effects of chemicals on human reproduction and the risks from exposure are often difficult to assess because of several factors (50). First, the human reproductive process is very complex, consisting of a wide spectrum of events and processes that must function normally to produce a healthy offspring. This spectrum begins with those events and processes necessary for impregnation of the female and extends to those necessary for birth of a normal offspring. Thus, the toxicity of reproductive system toxicants may encompass a wide diversity of effects such as, for example, alterations of sperm and egg production and activity, alterations of the uterine environment that affect implantation, adverse influences on normal placental function and interference with parturition. A second factor is the long span of years required for reproductive maturation, with the result that defects in an individual's reproductive function may not be detected for several years after exposure to a reproductive system toxicant. Finally, because of the considerable incidence of spontaneous defects in reproductive events and processes and of defects of genetic etiology, it is often difficult to separate these defects from those caused by environmental agents.

In recent years, reproductive system toxicants have become a major health concern because incidences of chemically induced germ cell damage and sterility appear to be on the increase (50). For example, male factory workers occupationally exposed to 1,2-dibromo-3-chloropropane (DBCP) in the

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United States were found to be sterile, evidencing oligospermia, azoospermia and germinal aplasia. There is also evidence that factory workers in battery plants in Bulgaria, lead mine workers in Missouri, U.S.A. and workers in Sweden who handle organic sovents, such as toluene, benzene and xylene, suffer from low sperm counts, abnormal sperm and varying degrees of infertility. In addition, diethylstilbestrol (DES), hexafluoroacetone (HFA), borax, cadmium, methylmercury and many cancer therapeutic agents have been reported to be toxic to the male and female reproductive systems and possibly capable of causing genetic damage to germ cells (51, 52).

In addition to these drugs and chemicals, which have been identified as causing abnormal reproductive function in humans, a large number of chemicals have been found experimentally to be toxic to the reproductive systems of animals (50). These chemicals with "inferred toxicity" to humans are listed in Table II-8 (male reproduction) and Table II-9 (female reproduction). Although the extrapolation of experimental results with laboratory animals to humans is inexact, many of these chemicals have been reported to also affect human reproduction. However, almost all of these chemicals require further study to determine whether they are human reproductive system toxicants, and under what conditions, and how they produce their effects.

There is evidence that different chemicals may cause damage to gonads and their function by (1) direct action of toxicants on germ cells, (2) actions affecting accessory secretions of prostate and seminal vesicles in the male, or (3) inhibition of overall controlling mechanisms at either the gonads or the hypothalamic-pituitary level (50). Experimental studies with laboratory animals are used to assess the toxic effects of drugs and chemicals on reproductive function and the mechanism of these effects. For assessment of effects on male reproductive function, a variety of morphologic, biochemical and functional parameters are employed. Morphologic changes may be detected by examination of the external appearance of the genitalia and by pathological and histopathological examination of the testes, prostate, seminal vesicle, vas deferens, epididymins and adrenal and pituitary glands. Biochemical indicators of toxicity include a variety of well-established tests, including measurements of sperm respiration, synthesis rates of nucleic acids, affinity constants of androgen and gonadotropin receptors, and "marker

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TABLE II-8. INFERRED TOXICITY: MALE REPRODUCTION (50)

Steroids

Natural and synthetic estrogens (antiestrogens), androgens (antiandrogens), and progestins

Chemotherapeutic Agents

Alkylating agents—esters of methanesulfonic acid (MMS, EMS, busulfan); nitrosoureas (CCNU, BCNU, MNU); hydrazines (procarbazine); ethylenimines (TEM, TEPA); nitrogen mustards (cyclophosphamide); others (mitomycin C)

Antimetabolites—folic acid antagonists (methotrexate); nucleic acid analogs (6-MP, 5-FU, azauridine, cytosine arabinoside)

Antitumor antibiotics—dactinomycin, daunomycin, adriamycin, bleomycin

Miscellaneous—vinca alkaloids (vincristine, vinblastine)

Other Therapeutic Agents

Psychopharmacologic agents—reserpine, phenothiazines, monoamine oxidase inhibitors

Adrenergic blocking agents—guanethidine

Diuretics—thiazides, spironolactone

Anti-infective agents—hycanthrone, nitrofuran derivatives

Volatile anesthetics—halothane, methoxyflurane

Oral hypoglycemia agents—chlorpropamide

Chronic alcoholism—tetraethylthiuram disulfide (antabuse)

Trace Elements

Cadmium, mercury, methylmercury, boron, lead

Insecticides

Organochlorine derivatives—O chlorophenothane (DDT), dieldrin, chlordane, benzene hexachloride, chlordecone (kepone)

Organophosphates—chlolinesterase inhibitors

Carbamates—carbaryl

Other Pesticides

Herbicides—chlorinated phenoxyacetic acids (2,4,-D, 2,4,5-T), diquat, paraquat

Fungicides—ethylene dibromide, 1,2 dibromo-3-chloropropane (DBCP), dithiocarbamates

Fumigants—ethylene dibromide

Food Additives and Contaminants

Cyclamate, nitrofuran derivatives, diethylstilbestrol (DES), aflatoxins

Industrial Chemicals

Volatile solvents—benzene, toluene, xylene

Alcohols—ethanol

Monomers—vinyl chloride

Chlorinated hydrocarbons—polychlorinated biphenyls (PCBs), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), hexafluoroacetone

Miscellaneous

Radiation—alpha, beta, and gamma radiation; x-rays

Stable isotopes—deuterium oxide

Physical factors—heat

TABLE II-9.   INFERRED TOXICITY: FEMALE REPRODUCTION (50)

Steroids

    Natural and synthetic estrogens, androgens, and progestins

Miscellaneous Drugs

    Reserpine, phenothiazines, amphetamine, serotonin, monamine oxidase inhibitors, antineoplastic agents (cyclophosphamide)

Organochlorine Derivatives

    Chlorophenothane (DDT) and derivatives

Organophosphates

    Parathion and derivatives (cholinesterase inhibitors)

Carbamate Insecticides

    Carbaryl

Food Additives and Contaminants

    Cyclohexylamine, nitrosamines, nitrofuran derivatives (AF_2), diethylstilbestrol (DES)

Industrial Chemical and Pollutants

    Polychlorinated biphenyls (PCBs), phthalic acid esters (DEHP)

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enzymes" of normal cellular differentiation. Other tests of male reproductive function evaluate accessory cell function, hormonal status, sperm morphology and activity and function of spermatogenic cell populations. Finally, mating studies are conducted to provide information on effects of chemicals on reproductive behavior and function.

    Tests for assessment of toxic effects on female reproductive capacity in animals also include morphologic, biochemical and functional parameters but are less extensive than for the male (50). In addition to inspection of the external genitalia, the vagina, cervix, fallopian tubes, ovaries, adrenal and pituitary glands should be subjected to gross pathological and histopathological examination. Biochemical assessment of toxicity to the female reproductive tract is made by study of nuclear and cytoplasmic

steroid receptors, measurements of biosynthesis of hormones and analyses of vaginal and uterine lumen fluid. For example, metabolites of dichlorodiphenyl-trichloroethane (DDT), dimethylbenz(a)anthracene (DMBA) and polychlorinated biphenyls (PCBs), and similar aromatic foreign chemicals have been reported to bind to the cytoplasmic receptor for estrogen. Such interactions between xenobiotics and cellular receptors for endogenous hormones may result in an inadvertent hormonal response or depress normal hormonal balance, thereby causing reproductive abnormalities. Other tests of female reproductive function evaluate accessory cell function, hormonal status and, finally, reproduction toxicity studies by which the ability of the female to conceive, the outcome of pregnancy and the viability and postnatal development of the offspring are assessed.

Reproduction toxicity studies in animals are designed to yield information on effects of chemicals on three segments of reproductive function, i.e., fertility, gestation and offspring. Effects of toxicants on fertility are reflected by toxicity in the parent male or female or both and may be the direct result of altered gonadal function, estrus cycles, mating behavior, conception rates and on the early stages of gestation such as effects on implantation of the fertilized ovum. In the second segment of the test, the development of the fetus and its degree of normality are evaluated in order to assess the toxic, teratogenic and mutagenic effects of chemicals. The last segment of the study is concerned with effects on the mother, such as effects on lactation and acceptance of offspring, and on the offspring with respect to its growth development and sexual maturation.

Teratogens are defined as substances that cause defects of fetal development (53). In the United States, some 200,000 birth defects are recorded each year, accounting for about 7 percent of all live births (54). In addition, more than 560,000 infant deaths, spontaneous abortions, stillbirths and miscarriages due to defective fetal development are recorded. It is estimated that from 1 to 5 percent of congenital defects in the human are drug or chemical related (55). However, incidence figures are often underestimated because a great variety of congenital defects and disorders are not detectable during early postnatal life.

It has been well established from human experience and animal experiments that susceptibility to teratogenic agents varies with the development stage at the time of exposure (53). This variation in susceptibility is due to the fact that embryogenesis is a precisely programmed sequence of cell proliferation, differentiation, migration and organogenesis. Figure II-2 shows a graphic display of the developmental sequence of human embryonic and fetal growth. The critical periods during human development consist of an embryonic period and a fetal development period, with most organogenesis completed during the first trimester. During the earliest stage of development, the first two weeks, rapid cell proliferation occurs and this activity is not generally disturbed by teratogens except that any damage may result in early death of the embyo. The next seven weeks is the embryonic period with early organogenesis in progress, and it is during this period that most major morphologic abnormalities may be produced by exposure to teratogens. The fetal period extends from the eighth week to full term and, during this period, physiologic defects and minor morphologic abnormalities may be produced by exposure to teratogenic agents. The most prominent example of a teratogen causing specific alterations during specific times of gestational development is thalidomide. This drug was found to be teratogenic when taken during gestational days 34 through 50, with the type of anomaly determined by the specific days of exposure. For example, ear anomalies were usually associated with intake between the thirty-fourth and thirty-eighth days, arm anomalies with intake between the fortieth and forty-fourth days and aplasia of the femur or tibia with intake between the forty-fourth and forty-eighth days.

All teratogenic agents act selectively on developing cells and tissues to initiate abnormal embryogenesis, inducing many of the early changes at a molecular or subcellular level, but they vary in their mechanisms of selectivity (53). Some teratogens are directly cytotoxic, acting specifically on cells in cycle. Acutely toxic doses of these drugs or chemicals may cause cellular death and even result in fetal death. Survivors may show symptoms of damage to systems that contain cells in cycle and with a short cycle time. Chronic administration of low doses may produce cellular abnormalities in several systems.

← Embryonic Period (in weeks) →						← Fetal Period (in weeks) → Full Term				
1 2	3	4	5	6	7	8	12	16	20-36	38

Period of dividing zygote, implantation, and bilaminar embryo

Central nervous system
Heart
Arms
Eyes
Legs
Teeth
Palate
External genitalia
Ear

Usually not susceptible to teratogens

| Prenatal death | Major morphologic abnormalities | Physiologic defects and minor morphologic abnormalities |

FIGURE II-2.   SCHEMATIC REPRESENTATION OF HUMAN DEVELOPMENT AND SENSITIVE PERIODS FOR PRODUCTION OF MALDEVELOPMENT.   CROSS-HATCHING REPRESENTS HIGHLY SENSITIVE PERIODS; CLEAR AREA REPRESENTS STAGES THAT ARE LESS SENSITIVE TO TERATOGENS (53).

Cytotoxic teratogens have been grouped according to their mechanisms of action such as alkylating agents, electrophilic reactants, antimetabolites, intercalating agents, amino acid antagonists and spindle poisons (53). For example, nitrogen mustards, sulphonoxyalkanes, ethylenediamines and epoxides are alkylating agents and are very reactive with molecules that have negative charges (nucleophiles), such as ionized carboxylic and phosphoric acids and thiols, or have negative areas due to the presence of amine groups. Consequently, these agents react with many biologic constituents, including nucleic acids, proteins, nucleotides and amino acids. Other cytotoxic teratogens require metabolism or bioactivation to electrophilic reactants to produce their effects. Examples of these drugs and chemicals include acetylaminofluoroene, aminoazobenzene, benzanthracenes, carbon tetrachloride, ethionine and nitrosourea. Antimetabolites (aminopterin, azauracils, mercaptopurine and halogenated pyrimidines) exert their cytotoxic effects by inhibiting pathways of purine or pyrimidine biosynthesis and formation of thymidylic acid. Intercalating agents (acriflavine, chloroquine and quinacrine) insert between base pairs of DNA and interfere with transcription and replication to produce cytotoxic effects. Amino acid antagonists (aspara-

ginase, azaserine and p-fluorophenylalanine) inhibit protein and nucleic acid synthesis by interfering with incorporation of specific amino acids required for protein or nucleic acid synthesis. Specific interference with asparagine, aspartic acid, glutamine, methionine, phenylalanine and tyrosine utilization has been reported. Finally, spindle poisons (colchicine, griseofulvin and vincristine) induce cytotoxicity by condensing with microtubular protein and interfering with formation of cellular organelles and the spindle apparatus.

Other proposed mechanisms of action of teratogens, in addition to direct cytotoxicity, are alterations in precursor and substrate availability (53). These alterations may affect chromosomes, alter energy sources, change membrane characteristics, or produce osmolar imbalance or enzyme inhibition. One common mechanism of teratogenesis is mutation. This defect is heritable and results from changes in the sequence of nucleotides of DNA, causing information encoded in DNA to be erroneously transcribed into RNA and ultimately into proteins. If the effect is in a germinal cell, the mutation will be hereditary, but if the effect is in a somatic cell, it will be transmitted to all descendants of that cell, but will not be hr editary. Somatic mutations in the early embryo may affect enough progeny ɔlls to produce a demonstratable structural or functional defect. Examples of agents or conditions that cause mutations are ionizing radiation, nitrous acid, alkylating agents, many carcinogens and other factors leading to chromosomal breaks or crossovers (56).

Another mechanism of teratogenesis is the lack of precursors and substrates needed for biosynthesis (53). Biosynthesis can be altered by specific dietary deficiencies of vitamins and minerals, which may be teratogenic, embryocidal or growth inhibiting to offspring of pregnant mammals. Deficiencies of essential materials can occur even with adequate supplies of such materials in the maternal diet. For example, the presence of analogs or antagonists to vitamins, essential amino acids, purines or pyramidines may result in the utilization of abnormal metabolites in biosynthesis instead of normal precursors. If these analogs or antagonists are incorporated in the biosynthetic process, abnormal development or death of early embryos may occur (57). Even when there are adequate supplies of normal precursors and substrates in the maternal diet, these materials may not be absorbed from the maternal digestive tract or transported across the placenta. Failure of

absorption from the maternal gut has been reported for copper due to excess zinc or sulfate and for iodine in the presence of high calcium (58). Azo dyes have been reported to inhibit placental transport in animals, thereby interfering with the transfer of materials essential for normal embryonic growth and causing a nutritional teratogenic deficiency (59, 60). Other teratogenic mechanisms (and agents) are alterations of energy supplies (iodoacetate), interference with enzyme function (5-fluorouracil, hydroxyurea), osmolar imbalance (trypan blue) and alterations of membrane characteristics (dimethyl sulfoxide).

A wide variety of drugs, chemical agents, dietary and hormonal deficiencies, vitamin and hormonal excesses, physical agents and microorganisms have been studied and reported to be teratogenic in animals (53). A comprehensive listing of these teratogens is presented in Table II-10. Information on human teratogens is less extensive and definitive because of the unavailability of human experimental data. In addition, often the birth of a defective child is attributed by the mother to some unusual event during pregnancy, which prejudices objective retrospective investigations into possible causative factors prior to the gestational period. Thalidomide is, of course, the most notorious of the human teratogens, having caused deformities in approximately 10,000 infants (53). After the thalidomide episode, investigations of the teratogenicity of drugs and chemicals intensified but, at present, only a few drugs have been identified as teratogens in man. Several other drugs and chemicals are suspected teratogens in humans as a result of animal studies or clinical suspicion. All cytotoxic anticancer drugs, such as alkylating agents, antimetabolites, plant alkaloids and antibiotics have the ability to block biosynthetic processes necessary for cellular replication, to act directly on DNA or to inhibit cell division. These substances, therefore, may be expected to cause fetal death or a wide variety of developmental abnormalities if administered during the critical period of organogenesis. Also, the drug, aminopterin, which is a folic acid antagonist and has been used as an abortifacient, is a human teratogen. Fetuses that survive exposure to this drug during the first trimester present a typical malformation syndrome, which includes hydrocephalus, absent or partially ossified skull bones, palate defects and other anomalies. Progestational steroids, which are used to treat habitual abortion, have produced masculinization of the female fetus and are contraindicated during suspected pregnancy (61). Methyl mercury ingestion by

TABLE II-10.   TERATOGENS IN ANIMAL MODELS (53)

Dietary deficiency: vitamins A, D, and E, ascorbic acid, riboflavin, thiamine, nicotinamide, folic acid, pantothenic acid, trace metals (Zn, Mn, Mg, Co), protein

Hormone deficiency: pituitary, thyroid, insulin (alloxan diabetes)

Vitamin antagonists: antifolic drugs, 6-aminonico-tinamide, 3-acetylpyridine

Hormone antagonists: thiouracil derivatives

Vitamin excess: vitamin A, nicotinic acid

Hormone excess: cortisone, hydrocortisone, thyroxine, vasopressin, insulin, androgens, estrogens, epinephrine

Carbohydrates: galactose, 2-deoxyglucose, bacterial lipopolysaccharides

Antibiotics: dactinomycin, penicillin, tetracyclines, streptomycin

Sulfonamides: hypoglycemic sulfonamides, sulfa-nilamide

Heavy metals: methyl mercury, phenylmercuric acetate, inorganic mercury salts, lead, thallium, strontium, selenium, chelating agents (EDTA)

Azo dyes: trypan blue, Evans blue, Niagara sky blue 6B

Agents producing hypoxia: carbon monoxide, carbon dioxide, etc.

Drugs and chemicals: nicotine, eserine, quinine, pilocarpine, ricin, saponin, chlorpromazine and derivatives, thiadiazole, triazene, boric acid, salicylate, hydroxyurea, acetazolamide, chlorcyclizine, meclizine, thalidomide, rauwolfia, vinca, veratrum alkaloids, triparanol (MER-29), serotonin, imipramine, 2,3,4,8-tetrachlorodibenzo-p-dioxin, nitrosamines, caffeine, barbital, carbutamide, diphenylhydantoin, amphetamine, glutethimide, morphine (Schardein, 1976; Shepard, 1976)

Insecticides, herbicides, fungicides

Solvents: dimethyl sulfoxide, chloroform, 1,1-dichloroethane, carbon tetrachloride, benzene, xylene, cyclohexanone, propylene glycol, alkane, sulfonates, acetamides, formamides

Natural substances: rubratoxin B, aflatoxin B_1, ochratoxin A, ergotamine, locoweed, jimson weed

Physical agents: hypo- and hyperthermia, hypoxia, radiation

Infections: 10 viruses known, including rubella and cytomegalovirus, syphilis, gonorrhea

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pregnant women has produced cerebral palsy in offspring, even though symptoms of poisoning were absent in the mothers (62).   Also, certain microorganisms have been identified as teratogens.   For example, toxoplasmosis and syphilis during pregnancy produce fetal malformations by direct invasion and destruction of fetal tissue (63).   Rubella infection during pregancy produces cataracts and other eye abnormalities, deafness, cardiac defects and mental retardation.   In fact, it has been reported that approximately 20 percent of women who contract rubella during the first trimester will give birth to a defective child.

In addition to the known teratogens, a considerable number of other drugs and chemicals are suspected of producing teratogenicity in humans. Drugs include anticonvulsants, anorexogenics, oral hypoglycemics and alkylating agents (55). Included among the possible teratogens are aspirin, antibiotics, antituberculous drugs, quinine, imipramine and insulin. Also, barbiturates, diphenylhydantoin, dextroamphetamine, antacids, nicotinamide, iron and antihistamines have been classified as suspected carcinogens by Catz and Abuelo (64) and several other drugs, including sulfonamides, cortisone, dicoumarol, excess vitamins A and D and LSD have been frequently mentioned or classified by other investigators as possible human teratogens. Results of studies conducted during the past 10 to 15 years have suggested that ethanol is a human teratogen (65, 66). These studies have shown that some children born to alcoholic mothers have pre- and postnatal growth failure, microencephaly, developmental delay and other anomalies, which have been termed the "fetal alcohol syndrome." In such cases, the growth rate appears to be irreversibly reduced, with the result that infants with this syndrome remain small and mentally defective. The teratogenic anomalies associated with ethanol excess during pregnancy appear to be due to the ethanol rather than malnutrition because linear growth is curtailed more than weight growth. In cases of generalized maternal malnutrition, fetal weight is curtailed more than linear growth.

Chemicals which are considered teratogens include insecticides, herbicides, fungicides, metals and solvents (67). Exposure to these chemicals generally occurs as a result of contamination of the general environment or through occupational contact. Evidence of teratogenciity of these chemicals has been demonstrated in animal models or from statistically derived human data. One of these chemicals is dioxin, which is a contaminant of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) widely used in agriculture and as a defoliant for military purposes. This chemical has been reported to be a potent mutagen, carcinogen and teratogen. Also, the fungicide, captan, is teratogenic. Metallic environmental pollutants that have been associated with teratogenic effects include methyl mercury and lead. The central nervous system of the fetus appears to be especially sensitive to the effects of methyl mercury. Children of pregnant women, who have been exposed to doses of this chemical without incurring typical symptoms of poisoning,

have developed cerebral palsy and other neurologic abnormalities such as chorea, ataxia, tremors, seizures and mental retardation (68).

In addition to teratogenic effects resulting from drug and chemical exposure, overt toxicity to the human fetus may result from drug and chemical administration in late gestation or at birth (53). The toxic effects to the fetus of a wide variety of drugs and chemicals are shown in Table II-11. Some of these effects may be produced in the fetus during the late gestational development or during parturition, some effects may occur during neonatal life and others may become manifest much later.

II.3 Routes of Entry of Toxicants

II.3.1 Introduction

In order for a chemical to produce a toxic effect, it must come in contact with the body or, more specifically, with a body membrane such as that of the skin, lungs or gastrointestinal tract. When the chemical comes in contact with the membrane, it may not be absorbed and may produce only a local effect. Alternatively, the chemical may be absorbed through the membrane into the bloodstream and act systemically on some target organ remote from the point of entry. Toxicants usually enter the bloodstream after absorption from either the skin, lungs or gastrointestinal tract. These are the three major routes of entry of chemicals into the body.

II.3.2 Skin Absorption

The most common exposure of man to foreign chemicals is by exposure through accidental contact of the chemical with the skin. The exposure may occur either by airborne chemical vapor or aerosol or by direct skin contact with the liquid or solid form of the chemical. Fortunately, the skin is not highly permeable and, therefore, provides a barrier that separates man from toxic substances. However, many chemicals can be absorbed by the skin in sufficient quantities to produce systemic effects. In order to be absorbed, the chemical must either pass through the epidermal cells, the cells of the sweat glands or the sebaceous glands or enter through the hair follicles. The pathway through the epidermal cells appears to be the main avenue of penetra-

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TABLE II-11. DRUG AND CHEMICAL TOXICITY IN THE HUMAN FETUS (53)

Alcohol	Muscular hypotonia, withdrawal
Antibacterials	
Streptomycin	8th nerve damage
Tetracyclines	Deposition in bone, discoloration of teeth, inhibition of bone growth
Sulfonamides	Kernicterus, anemia
Novobiocin	Hyperbilirubinemia
Chloramphenicol	Death (gray syndrome)
Erythromycin	Liver damage
Nitrofurantoin	Hemolysis
Anticoagulants	
Coumarin	Hemorrhage, death
Sodium warfarin	
Antidiabetics	
Tolbutamide	Thrombocytopenia
Chlorpropamide	Prolonged hypoglycemia
Phenformin	Lactic acidosis
Insulin (shock)	Fetal loss
Ammonium chloride	Acidosis
Adrenocortical hormones	Adrenocortical suppression
Prednisolone	Acute fetal distress, fetal death
Antihistamines	Infertility
Antithyroid drugs	Hypothyroidism
Barbiturates, diphenylhydantoin	Coagulation defects, withdrawal syndrome (barbiturates only)
Phenobarbital excess	Neonatal bleeding, death
Chlordiazepoxide	Withdrawal syndrome
Diazepam	Hypothermia
Meprobamate	Retarded development
Sedatives	Behavioral changes
Meperidine	Neonatal depression
Primidone	Withdrawal syndrome
Heroin, morphine, methadone	Withdrawal syndrome, neonatal death
Mepivacaine	Fetal brachycardia and depression
Reserpine	Nasal congestion, lethargy, respiratory depression, brachycardia
Phenothiazines	Hyperbilirubinemia, depression, hypothermia
Hexamethonium bromide	Neonatal ileus
Cholinesterase inhibitors (pesticides)	Transient muscle weakness
Magnesium sulfate	Central depression and neuromuscular block
Quinine	Thrombocytopenia
Iophenoxic acid	Elevation of serum PBI
Chloroquine	Death
Alphaprodine	Platelet dysfunction
Thiazide diuretics	Thrombocytopenia, salt and water depletion, neonatal death
Lithium	Cyanosis and flaccidity
Primaquine, pentaquine	Hemolysis

Vitamin K analogs, excess	Hyperbilirubinemia
Intravenous fluids, excess	Fluid and electrolyte abnormalities
Smoking	Premature birth, small babies, perinatal loss
Vaccinations	Fetal vaccinia
Polio vaccine, live	Fetal loss
Oral progestins, androgens, estrogens	Advanced bone age
Salicylates, large amounts	Bleeding
Anesthetics (general anesthetics)	Newborn depression
Solvents	Newborn depression

tion for most chemicals because the epidermal tissue constitutes the major surface area of the skin.

The physicochemical properties of a chemical are the principal determining factors with respect to the extent and rate of absorption of the chemical through the skin. These include such properties as the pH of the chemical, the extent of its ionization, its molecular size, and the water and lipid solubility of the compound. Polar and nonpolar chemicals are believed to penetrate the epidermal layer of the skin by different molecular mechanisms, and nonpolar compounds tend to penetrate more readily than polar species. In the case of the nonpolar chemicals, the rate of penetration appears to be directly related to the lipid solubility of the chemical and inversely related to its molecular weight (69). Finally, injury or removal of the stratum corneaum layer of the epidermis by agents such as acids and alkalis or alteration of its permeability by chemicals such as dimethyl sulfoxide (DMSO) can cause an increase in the permeability of the epidermis. The increased permeability may facilitate penetration of all kinds of molecules, large or small, lipid soluble and water soluble (70).

The importance of the percutaneous route for entry of chemicals into the body in sufficient concentrations to cause serious toxic effects cannot be overemphasized. The American Conference of Governmental Industrial Hygienists (ACGIH) has recognized the potential toxic contribution of this route to the overall exposure of an individual. Substances which are readily absorbed through the skin are identified by a "Skin" notation in the ACGIH listing of Threshold Limit Values (TLVs). The intent of this notation is to suggest the adoption of appropriate measures for the prevention of cutaneous absorption so that the allowable atmospheric concentration is not invalidated because of absorption through the skin. Examples of chemicals identifed by the ACGIH are phenol, methyl alcohol, methyl bromide, n-butyl alcohol, carbon tetrachloride and acrylonitrile.

Even when foreign chemicals come in contact with the skin and are not absorbed, any of several dermal toxic reactions to the chemical may result. Chemicals that readily react with tissue components cause direct injury to the skin, which is sometimes referred to as a local irritant action,

an etching action or a necrotic action, depending on the reactivity of the substance. Strong alkaline solutions such as sodium hydroxide and potassium hydroxide solutions produce an etching action. Concentrated nitric acid causes not only a strong local alteration of pH but also oxidizes and causes nitration of components of the skin. Other chemicals that cause direct skin damage include nitrogen mustards and related biological alkylating agents (vesicants) and keratolytic agents, especially phenols, such as salycylic acid. Organic solvents remove protective sebaceous layers in the skin, thereby facilitating the development of allergic dermatoses and chemical dermatitis.

Other dermal reactions to foreign chemicals include allergic or sensitizing reactions, hypersensitivity, photoallergic reactions, photosensitization and phototoxic reactions. Under certain circumstances, practically any chemical can cause an allergic reaction, its occurrence being dependent on the constitution of the individual and on the properties of the substance. Some compounds, such as dinitrochlorobenzene, produce allergic reactions in almost everyone exposed to them while other chemicals produce reactions only occasionally. These allergic or sensitization reactions involve an immune mechanism and require preconditioning of an individual to the chemical (see Section II.2.9). Hypersensitivity, which is sometimes incorrectly referred to as sensitization, is a normal toxicologic response of greater intensity than that exhibited by most of the population. Other chemicals (tetrachlorosalicylanilide, hexachlorophene and bithionol), when present in the skin, may undergo photochemical alterations to allergenic products. Once this allergic sensitization occurs, exposure to sunlight will produce a skin reaction whenever the skin is exposed to the substance. In contrast to photoallergic reactions, photosensitization results from a combined exposure to certain chemicals and sunlight and can occur even upon the first contact with the chemical and exposure to sunlight. The substance in the skin may be converted into a toxic product by a photochemical reaction influenced by the sunlight and result in a phototoxic reaction. The nature of the symptoms produced depends on the kind of toxic product that is formed.

II.3.3   Inhalation

Exposure to chemicals in the atmosphere often results in their inhalation and absorption from the alveoli of lungs into the body. In order for any chemical to reach the alveoli of the lungs, it must be either a gas, a vapor, or of sufficiently proper particulate size so that it is not removed in the airways to the lungs. Examples of toxicants that are absorbed by the lungs are gases such as carbon monoxide, sulfur dioxide and hydrogen sulfide, vapors of volatile liquids such as benzene, toluene and methanol and aerosols such as silica. An aerosol is a relatively stable suspension of solid particles or liquid droplets in a gaseous medium. Gases or vapors are frequently adsorbed on the surface or dissolved in aerosols. Traditionally, terms such as dusts, fumes, smokes, mists and fogs have been used to describe aerosols.

Deposition of particles in the respiratory tract may occur by interception, impaction, sedimentation and diffusion. These processes have been described in detail by Menzel and McClellan (2). The site of deposition of particles in the respiratory tract affects 1) the severity of tissue damage and its consequence˙, 2) the extent of absorption of systemic toxicants and 3) the clearance mechanisms available for removal of the particles. The nature of the interaction of physical and biologic factors that influence the regional deposition of particles is illustrated in Figure II-3. For very small particles (<1 um), which are deposited in small airways and in the alveoli primarily by diffusion, the critical factor in regional deposition is the particle size. For particles that are deposited by impaction and sedimentation, the aerodynamic diameter primarily determines the site of deposition. This diameter, which is used to characterize particles that are non-spheric in shape, takes into account both the density of the particle and its aerodynamic drag. Particles having an aerodynamic diameter of 5 to 30 um are largely deposited in the nasopharyngeal region by impaction. The high air velocity and tortuous nature of the nasopharyngeal air passages provide an ideal area for impaction. Those particles with an aerodynamic diamter of 1 to 5 um are deposited in the tracheobronchial regions by sedimentation. This mechanism of deposition is favored by the slower airflows, which allow time for deposition by gravitational forces. As the alveolar regions are approached, the airflow velocity decreases markedly, allowing even more time

for sedimentation. The small particles (<1 ɪm) that have penetrated to these regions are deposited primarily by diffusion.

Particle deposition may be influenced by physiologic or patho-logic factors (2). One important factor iɔ the pattern of breathing. During quiet breathing, a large proportion of inhaled particles may be exhaled be-cause the tidal volume is only two to three times the volume of the dead space. During exercise, however, larger volumes are inhaled at higher veloci-ties and impaction in large airways and sedimentation and diffusion in smaller airways and alveoli will increase. Also, factors that modify the diameter of conducting airways can modify particle deposition. For example, in patients with chronic bronchitis, the thickened mucous layer may partially block air-ways in some areas. Jets formed by the air flowing through these partially occluded airways may increase deposition of particles by impaction and turbu-lent diffusion in the small airways. Tracheobronchial deposition of particles would tend to increase following inhalation of materials that produce vasocon-striction. Cigarette smoking has been shown experimentally to produce such an effect (71).
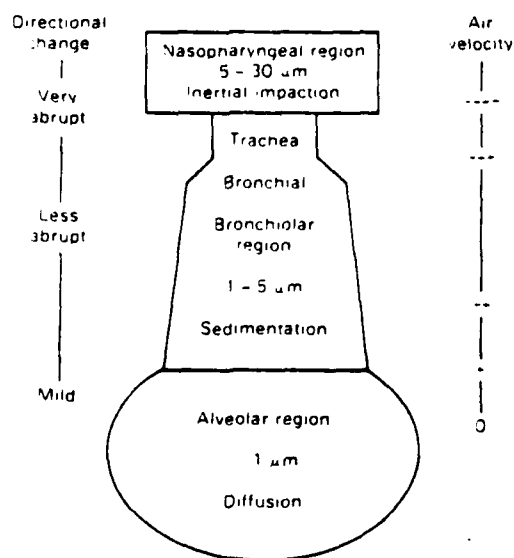
FIGURE II-3. PARAMETERS INFLUENCING PARTICLE DEPOSITION (2).

Particles that have been deposited on the surface of the respiratory tract are removed by mechanisms that vary with the site of deposition (2). The speed and efficiency of these clearance mechanisms are critical factors in the toxic potential of these inhaled materials. Rapid removal decreases the time available for the toxicant to cause critical damage to tissues of the respiratory tract or to be absorbed systemically and cause injury to other target organs. The primary mechanism of clearance of particles from the ciliated surfaces of the respiratory tract, which extend from the terminal bronchioles to the nose, is mucociliary transport. This transport process, involving the ciliated epithelial cells and the mucous layer on their surface, moves the deposited material to the oral cavity where it is then ingested. In the human nose, trachea and upper bronchial tree, particles are moved at relatively high velocities and the ciliated surfaces may be cleared in a matter of hours (72, 73). However, there are reports of absorption of certain chemicals from these surfaces into the bloodstream, indicating that not all material deposited on the ciliated surfaces is cleared via the mucociliary process.

In the pulmonary region, there are three primary avenues by which deposited particulate material may be removed: 1) particles may be phagocytized and cleared up the tracheobronchial tree via the mucociliary escalator; 2) particles may be phagocytized and removed via the lymphatic drainage; and 3) material may dissolve from the surfaces of particles and be removed via the bloodstream or lymphatics (2). In addition, particles and some dissolved material may be sequestered in the lung. In the alveolar region of the lung, the large numbers of macrophages function to phagocytize and remove particulate. Within minutes after particles are inhaled they may be found within alveolar macrophages, and almost all particles are engulfed within a matter of hours. Many of the alveolar macrophages are ultimately transported to the mucociliary escalator but the means of transport is not known. One of the most accepted theories is that the alveolar macrophages move via ameboid motion to the level of the respiratory bronchiole for further mucociliary transport. Other macrophages with ingested particles have been observed in the interstitial tissue spaces of the lung within hours after particles are inhaled and in the lymphatics and lymph nodes that drain the lung within a matter of days after inhalation of the particulate. For most

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materials deposited in the alveoli, however, dissolution and removal of the solute are probably the most significant processes by which material is removed from the lung (74, 75). The rate at which particles are dissolved are believed to depend primarily on their surface areas and the dissolution rates of the particular physicochemical form of the materials.

The alveolar region of the respiratory tract is the primary site where inhaled toxicants are absorbed. The surface area of the alveoli is large and blood flow to the lung is high and close to the alveolar air so that many toxicants are readily absorbed. However, the rate of absorption of gases and vapors is variable and dependent on the toxicant's blood:gas solubility. If the gas vapor has a very low solubility, the rate of absorption is highly dependent on the blood flow through the lung (perfusion limited). For gases or vapors with a high solubility, the rate is highly dependent on the rate and depth of respiration (ventilation limited). In addition to gases and vapors, liquid aerosols and particles are often absorbed in the alveoli. Liquid aerosols, if lipid soluble, will readily pass the alveolar cell membranes. The mechanisms of absorption from the alveolar surfaces are poorly understood. Studies with a number of drugs in aqueous solution have demonstrated that absorption is mediated by a nonsaturable process of diffusion, which is extremely rapid. Absorption rates are related to the molecular size: the higher the molecular weight, the slower the rate of absorption (76). As a rule, gases and vapors of volatile liquids are small molecules that readily cross the alveolar epithelium. Analysis of absorption rates of known compounds suggests that the pulmonary epithelium contains at least three different types of pores, which allow only molecules of a certain size to pass and thereby influence the absorption rate of a chemical (77). In addition to diffusion, there also appears to be a specific carrier-type transport system that is saturable and is shared competitively by a number of organic anions (76).

The potential hazards associated with the absorption of chemicals by the lungs are particularly evident in industrial working environments. In these environments, there exists the opportunity for exposure of workers to a multitude of toxic chemical gases, vapors and aerosols. Because of the potential hazards of such exposures, environmental standards have been

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established for airborne chemicals and dusts in order to protect the health and safety of industrial workers. Each year the American Conference of Governmental Industrial Hygienists (ACGIH) compiles and publishes a list of Threshold Limit Values (TLV's), consisting of several hundred chemicals and substances to which workers may be exposed in the industrial environment. These limit values refer to airborne concentrations of substances and represent conditions under which it is believed that most workers may be exposed continuously during the usual 8-hour work schedule without adverse effects. Additional safety standards and guidelines for exposure of workers to chemical atmospheres are published by governmental agencies such as the Occupational Safety and Health Administration (OSHA) and chemical manufacturers.

II.3.4   Ingestion

Foreign chemicals may be absorbed from the mouth or from other areas of the gastrointestinal tract, mainly by simple diffusion. In general, absorption takes place along the entire length of the gastrointestinal (GI) tract, but the chemical properties of each substance determine whether that material will be absorbed in the strongly acid stomach or in the nearly neutral intestine. Gastric absorption is facilitated by an empty stomach, in which the compound has good access to the mucosal wall. The absorption of some chemicals is aided by the consumption of a fatty meal. Intestinal absorption is facilitated by the large surface area of the intestinal villi, the presence of bile and a rich blood supply. Tne principles governing the absorption of chemicals from the gastrointestinal tract are the same as those for passage of chemicals across biolgoical membranes elsewhere. A low degree of ionization, a high lipid/water partition coefficient of the unionized form and small molecular size of water-soluble substances facilitate rapid absorption.

Although the oral route of entry is an important route for drugs and in accidental ingestion of chemicals, it is generally not of major importance for occupational chemicals. In the occupational environment, the oral intake of foreign substances is likely to occur mainly from the ingestion of food or drink, or the smoking of cigarettes which may have been contaminated with chemicals due to improper sanitary practices. Oral ingestion could

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also occur as a result of the swallowing of inhaled particles that are transported out of the lung by mucociliary action.

II.4 Distribution, Metabolism and Excretion of Toxicants

II.4.1 Distribution

After a toxicant is absorbed into the bloodstream, it is available for distribution throughout the body. Distribution usually occurs rapidly, with the rate of distribution to the tissues of an organ determined by the blood flow through that organ and the ease with which the chemical crosses the capillary bed and penetrates the cells of the particular tissue. The eventual distribution of a toxicant is largely dependent on its ability to pass the cell membrane of various tissues and on the affinity of the various tissues for the chemical. Small, water-soluble molecules and ions apparently diffuse through aqueous channels or pores in the cell membranes, whereas lipid-soluble molecules readily permeate the membrane itself. Larger water-soluble molecules and ions (molecular weights of 50 or more) cannot enter cells easily except by specialized transport processes mediated by carriers or membrane components that form a complex with the substance to be transported. Those toxicants which do not readily pass through cell membranes are restricted in their distribution and in their potential effects in the body.

Some toxicants accumulate in various areas of the body as a result of binding, active transport or high solubility in fat. The accumulation may be at the site of major toxic action of the chemical, but, more often, it is in some other location. In the latter case, the accumulation may serve as a protective mechanism by distributing part of the toxicant into a storage depot and thereby reducing the concentration of the agent in the target organ. Although toxicologically inactive, the chemical in the storage depot is in equilibrium with free toxicant and is slowly released into the circulation as the free toxicant is metabolized or excreted from the body.

The major storage sites for toxicants in the body are plasma proteins, the liver, the kidney, fat and bone. Within the plasma, several proteins can bind foreign chemicals. Most toxicants that are bound to plasma

proteins are bound to albumin by reversible bonds. The large molecules of the plasma proteins prevent passage of the toxicant across capillary walls and tend to restrict the chemical to the vascular space. Thus, the fraction of the toxicant in the plasma bound to plasma proteins is not available for distribution into the extravascular space. Nor is this fraction available for filtration at the kidney. However, the interaction of a chemical is a rapidly reversible process and, as unbound chemical diffuses from the capillaries, bound chemical dissociates from the protein to maintain the plasma concentration in equilibrium with that in the extravascular water. The reversibility of this process is very important toxicologically because severe toxic reactions can result if the chemical is rapidly released from the plasma protein. It is possible for a second chemical to displace the toxicant from the plasma protein, thereby making it available in free form. In this way, a second chemical can induce toxicity from the first chemical. Although most of the research performed on the binding of xenobiotics to plasma proteins has been with drugs, other chemicals are known to bind to plasma proteins. It is likely that other chemicals may compete for the same binding sites and chemical-chemical interactions may result.

The liver and the kidney also have a high capacity to bind foreign chemicals and probably concentrate more toxicants than other organs. This capability is probably related to the roles of these organs in the elimination of toxicants from the body. Although the precise mechanism by which the liver and kidney remove toxicants from the blood has not been established, active transport and protein binding have been suggested as possible mechanisms. As an example of the rapidity with which the liver can bind foreign chemicals, 30 minutes after a single administration of lead, the hepatic concentration is 50 times higher than in the plasma (78).

Many industrial chemicals such as the chlorinated solvents are highly lipophilic and can readily penetrate cell membranes of tissues. Since they have a high lipid solubility, they can distribute and concentrate in body fat. The chemicals appear to be stored by simple dissolution in the neutral fats, which make up from approximately 20 percent of the body weight of a lean individual to 50 percent of the weight of an obese person. Thus, the storage in fat of a toxicant with a high lipid/water partition coefficient may lower

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the concentration in the target organ and serve as a protective mechanism. However, it is possible that a rapid mobilization of fat stored for energy could produce a rapid increase in the concentration of the chemical in the blood and in the target organ.

Bone can also serve as a storage area for chemicals, principally for fluoride, lead and strontium. Bone is a major site of storage for lead, with 90 percent of the lead in the body found in the skeleton. However, this tissue has importance as a depot for only a limited number of industrial chemicals.

II.4.2   Metabolism

The body has two major defense mechanisms for the removal of foreign chemicals. These are metabolism of the chemical and excretion of the chemical or its metabolic products. Since the metabolism of a toxicant involves its chemical transformation, the process has been referred to as "metabolic transformation" and "biotransformation" (39). Most foreign chemicals that enter the body undergo this process. However, some chemicals are also partially excreted from the body in an unchanged form in the expired air, urine, feces and/or perspiration. All of the biotransformation processes are enzymatically induced and result either in the alteration of the chemical molecule or the combination of the chemical with a normal constituent of the body. Generally these processes convert lipid-soluble chemicals into more water soluble species which are then more easily excreted by the body.

The enzyme systems in the body which metabolize foreign compounds are present in many tissues but are particularly abundant in liver cells. Thus, the liver is the major organ involved in the biotransformation of chemicals, although metabolism in other tissues (intestine, kidney, lung, brain and skin) is also known to occur. The enzymatic reactions, as proposed by Williams (79), may be divided into two types: Phase I reactions, involving oxidation, reduction and hydrolysis; and Phase II reactions, consisting of conjugation or synthesis. Phase I reactions generally convert foreign chemicals to derivatives that can then undergo Phase II reactions. The enzymes that carry out reactions of both types are sometimes referred to as "detoxifi-

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cation enzymes." However, this term is misleading because some chemicals are transformed into products that are more toxic than the parent compound. This is particularly true of some chemical carcinogens, organophosphate insecticides and a number of compounds, such as perchlorethylene, chloroform, carbon tetrachloride, and bromobenzene, that cause cell death in the lung, liver or kidney (80).

The most important enzyme systems involved in Phase I reactions (oxidation, reduction and hydrolysis) are the cytochrome P-450-containing monooxygenases. These enzyme systems, which are composed of two enzymes, are localized in the endoplasmic reticulum, a complex network of membranes within the cell that is continuous with the outer nuclear membrane. Examples of the types of reactions catalyzed by the cytochrome P-450-containing monooxygenases are aromatic hydroxylation, aliphatic hydroxylation, N, O, or S-dealkylation, epoxidation, desulfuration, sulfoxidation and N-hydroxylation. These reactions are shown in Table II-12. In addition, this enzyme system is also possibly involved in the reduction of azo and nitro compounds (81).

TABLE II-12. EXAMPLE OF THE GENERAL TYPE OF OXIDATION REACTIONS CATALYZED BY THE CYTOCHROME P-450-CONTAINING MONOOXYGENASES (80)

Other enzyme systems are involved in the metabolism of foreign chemicals but these are of lesser importance than the cytochrome P-450-con-

taining enzymes. Examples are amine oxidase, epoxide hydratase, esterases and amidases and alcohol and aldehyde dehydrogeneses. The reactions catalyzed by these enzyme systems are considered Phase I reactions.

Phase II reactions involve the synthesis of a derivative of a foreign chemical that is generally more water soluble and more easily excreted than the substrate. These reactions are generally referred to as conjugation reactions. The most common and one of the most important conjugation reactions is the synthesis of glucuronic acid derivatives of various substrates, which can be either foreign or endogenous compounds such as steroids or bilirubin. The enzyme that carries out this reaction is uridine diphosphate glucuronyl transferase (UDP - glucuronyl transferase). Although glucuronyl transferase activity is localized in the endoplasmic reticulum, mainly of the liver, activity has also been found in the kidney, intestine, skin, brain and spleen. Chemical groups that are capable of undergoing conjugation reactions with glucuronic acid include aliphatic and aromatic alcohols, some carboxyl groups, sulfhydryl groups, and primary and secondary aromatic and aliphatic amines. Other enzyme systems that carry out Phase II reactions are glutathione S-transferases, sulfotranferases, amino acid conjugases, methyl transferases and N-acetyl transferases.

Foreign chemicals may be toxic or be metabolized to products that are toxic. The rate of metabolism of these chemicals, whether to less or more toxic species, is of paramount importance to the overall toxicity of the chemical. A variety of factors may influence the rate of metabolism of any chemical that is absorbed into the body. For example, the rates of absorption, transfer across cell membranes and excretion of a chemical may influence either the concentration of the chemical at the active sites of enzymes involved in its metabolism or the time for interaction of the chemical or its products with target molecules in the organism. In addition, various physiologic factors may affect the rate of metabolism of foreign compounds in animals or man. These include the species, strain, sex and age of the animal. Other factors that may affect the rates of metabolism and toxicity of chemicals are the time of day (circadian rhythms), temperature, pregnancy, disease states and the nutritional status of the animal.

Perhaps the most important of all of the factors that affect the rate of metabolism of chemicals is the effect of other chemicals on the activities of the metabolizing enzymes. It has been well established that the activity of the hepatic cytochrome P-450-containing nonooxygenase systems, and of other enzymes, can be markedly increased in various animal species including man by exposure to a large number of drugs, pesticides and industrial chemicals. This process of increased activity of these enzyme systems is referred to as enzyme induction. A large number of foreign chemicals has also been shown to inhibit the cytochrome P-450 monooxygenase-catalyzed metabolism of other foreign compounds. Whether the induction or inhibition of these enzyme systems results in an increase or a decrease in the toxicity of a particular compound is dependent on the toxic properties of the compound in question. Induction of enzymes involved in metabolizing a chemical to less toxic products will generally result in a decrease in the toxicity of the compound. On the other hand, enzyme inhibition may lead to an increased toxicity due to increased half-life of the parent compound. The opposite effects should generally apply to compounds whose metabolic products are more toxic than the parent compound. This aspect of interactions between chemicals, as well as other factors that affect the toxicity of chemicals, are discussed in more detail in Section II.5.

II.4.3   Excretion

Although most foreign chemicals are metabolized before the metabolic products are excreted from the body, some are eliminated, at least partially, in unchanged form. Foreign chemicals, either as the parent compound or as metabolic products, are eliminated from the body by various routes. The major routes are exhalation by the lungs, fecal excretion via the liver and gastrointestinal tract and excretion by the kidneys. All body secretions such as perspiration, tears and saliva also appear to have the ability to excrete foreign compounds but these are minor routes of elimination.

The kidney is a very efficient and important organ for the elimination of toxicants from the body. Toxic compounds are excreted into the urine by the same mechanisms the kidney uses to remove the end products of the

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metabolism of food from the body. These mechanisms include glomerular filtration, tubular diffusion and tubular secretion. A chemical in the bloodstream will be filtered at the glomerulus of the kidney unless its molecular weight is large or it is bound to plasma proteins. Many toxic agents have molecules that are small enough to undergo passive glomerular filtration. When a chemical has been filtered at the glomeruli, it may remain within the tubular lumen and be excreted or it may be reabsorbed from the tubule back into the bloodstream. Those toxicants with a high lipid/water partition coefficient will be passively reabsorbed whereas polar compounds and ions will be excreted. The acidity of the urine may also affect the excretion of a chemical since the proportion of the compound in ionic form can be markedly altered by changes in pH of the urine. Toxic agents can also be excreted from the plasma by passive diffusion through the tubule into the urine and by active tubular secretion into the urine. The former mechanism is generally considered of only minor significance in elimination of toxicants from the body. The latter process, active secretion, is an active transport process and, in contrast to filtration, has the capability to remove protein-bound toxicants from the bloodstream.

The respiratory system may be an important excretory route for a number of toxicants. Many toxic agents that enter the body by the respiratory tract are also excreted by the same route. These include gases such as carbon monoxide as well as certain alcohols and other volatile agents which are partially excreted unchanged by the lungs. The rate of elimination of foreign gases from the lungs is inversely related to the rate of uptake of the gases by the lungs. Thus, gases, such as nitrous oxide, with a low blood/gas solubility are rapidly excreted by the lungs, whereas ethanol, with a higher blood/gas solubility, is excreted very slowly by the lungs. Particles also enter the respiratory tract and are deposited at different levels of the tract, depending primarily on their size and aerodynamic diameter. Other chemicals may be adsorbed on the surface of these particles and carried to the sites of deposition. Mechanisms by which the particles are removed from the respiratory tract include mucociliary transport, phagocytosis by macrophages and removal via the mucociliary escalator and phagocytosis and removal via the lymphatics of the lung. Substances adsorbed on the surface may, in addition, dissolve and be removed via the bloodstream or lymphatics. These mechanisms

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are discussed in greater detail in Section II.3.3.

Many chemicals or metabolites of these chemicals may also appear in the feces. These compounds are present in the feces because the chemical was orally ingested and not absorbed, it was excreted into the bile and/or it was excreted by the gastrointestinal tract.

Although many toxic chemicals may be absorbed into the body, the body has the ability to metabolize and excrete many of these compounds into the urine and bile. However, when the rate of absorption exceeds the rate of excretion, the toxicant may accumulate and attain a critical concentration in the body. When this occurs, toxic effects are produced. Therefore, any chemical or condition that disrupts the functional or structural integrity of the excretory organs may alter the toxicity of a foreign chemical. Such disruption may result from interference with ciliary transport and macrophage activity in the lung, with metabolism in the liver, with competition for secretory or reabsorptive processes in the kidney, and with fecal elimination of the toxic agent.

II.5 Factors Influencing Toxicity

II.5.1 Introduction

In order for a chemical to produce a toxic effect, it must be absorbed and enter the blood, unless it acts topically as, for example, a caustic agent. Once in the bloodstream, it is necessary for the chemical or its metabolites to reach an appropriate receptor in the biologic system at a sufficiently high concentration and for sufficient time to initiate the toxic effect. Thus, changes in dose or exposure concentration, route of entry and duration of exposure can markedly influence the biologic response to a single toxic agent. However, even when these factors are strictly controlled, there is still likely to be considerable variation among individuals in their response to a specific toxicant. This variation may be due to factors that influence the absorption, distribution, metabolism or excretion of the chemical or to any of a number of other factors. The major factors that may influence the toxicity of a chemical to an individual, and consequently the hazard

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of the chemical, are reviewed in the following subsections.

II.5.2 Physical and Chemical Properties

The physical and chemical properties of a substance are important factors in determining the potential toxicity and hazard of the substance. One of the most important properties of the chemical in the industrial environment is its vapor pressure, which determines the maximum equilibrium concentration of the chemical in the atmosphere. The ratio of the saturated vapor concentration of a chemical to its ACGIH TWA-TLV value has been used as a measure of the potential inhalation hazard and has been designated as the Inhalation Hazard Potential (IHP) (82). Other important physicochemical properties include lipid solubility, degree of ionization, pH, molecular size and, if in aerosol form, particle size. These properties affect the rate and extent of absorption and the distribution of chemicals in the body and, in this manner, are an important determinant of their potential toxicity. This subject was discussed in detail in preceding sections.

II.5.3 Environmental Factors

A number of environmental factors, including temperature, pressure, radiation and atmosphere oxygen content, are capable of influencing the biologic response of animals and man to foreign chemicals. Of these factors, temperature and oxygen levels are generally the most important in the occupational environment. The biologic response may also be altered by physical factors, such as vibration or noise, which can be considered environmental in nature. A comprehensive review of the effects of environmental factors on the toxicity of chemicals is contained in the U.S. Department of Transportation report entitled "Principles of Toxicological Interactions Associated with Multiple Chemical Exposures" (83).

One of the most important environmental factors is temperature. It is not surprising that both increased and decreased temperatures can influence toxic responses in animals and in man, considering that the processes of absorption, storage, metabolism and elimination are to some extent temperature-dependent. In addition, extreme low temperatures establish a

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condition of stress that may markedly alter the metabolism of drugs and foreign chemicals, principally by activation of hepatic microsomal enzymes. Examples of alterations of chemical metabolism by cold include the enhancement of hydroxylation of acetanilide and 2-naphthylamine (84). Low temperature also stimulates the metabolism of aniline, but depresses the hydroxylation of hexobarbital (85). Elevated environmental temperatures have also been observed to influence the response to toxic chemicals and drugs. For example, fluid loss resulting from heat stress (or exercise) may severely exacerbate the diuresis caused by inhibition of antidiuretic hormone (ADH) by ethanol, leading to serious consequences (86). Potentiation of sublethal toxicity by thermal stress has been reported for other drugs, ozone, certain metals, various pesticides and other chemicals (83); additional information can be found in reviews by Doull (86) and Weike (87). Low oxygen levels may also affect the toxicity of foreign chemicals, as evidenced by the abnormal response of hypoxic animals to chemical exposures. For example, in such animals, the metabolism of alcohol proceeds at a reduced rate and experimentally induced lung tumorigenesis is increased at reduced oxygen levels (88, 89).

Environmental temperature has also been reported to influence the thermoregulatory effects induced by ethanol (90). In the rodent, it is generally agreed that ethanol alters the animal's thermoregulatory ability and induces hypothermia. A dose-dependent relationship between the dose of alcohol administered and the decrease in body temperature has been found in both rats and mice (91, 92). In addition, the magnitude of the hypothermic response is potentiated at low ambient temperatures (Ta). In man, the thermoregulatory effects of ethanol and alterations in heat production and heat loss at different ambient temperatures are very controversial. Anderson et al. (93) found no change in the metabolic rates of men exposed acutely to Ta of 15° or 20°C following consumption of 1 gram of ethanol per kilogram of body weight. In contrast, Keatinge and Evans (94) reported that men exposed to Ta of 15°C exhibited a decrease in metabolic rate following intake of ethyl alcohol. As for heat loss, some investigators have reported an increase in peripheral vasodilation and have suggested that an increase in heat loss accompanied the acute administration of ethanol (91, 95-98). The results of other studies, however, indicate that there is little change in total heat

loss from man following intake of the alcohol at either cold (93, 99-101) or neutral ambient temperatures (102). Because of these inconsistencies, Fellows et al. (103) compared the thermoregulatory responses of human volunteers at two environmental temperatures, 21°C and 30°C. The investigators found that deep body temperature (core temperature) was only minimally reduced after the consumption of ethanol (0.5 - 1 g/kg body weight) and the fall in temperature was no greater at a Ta of 21°C than at 30°C. The vasodilation following ethanol ingestion, however, was significantly greater at a Ta of 30°C than at 21°C. Thus, the authors concluded that environmental temperatures do not have a marked effect on heat loss but can have a profound effect upon the vasodilation induced by ethanol ingestion and that inconsistencies in results reported in the literature were due to the temperatures under which the experiments were conducted. Despite the minimal fall in deep body temperature observed in these experiments, the investigators cautioned against the ingestion of ethanol by individuals who have been engaged in severe exercise. In subjects who ingested ethyl alcohol after a two-hour period of exercise, both hypoglycemia and hypothermia resulted, although ethanol, without exercise, induced neither condition (104).

Physical factors, such as vibration and noise, have also been reported to influence the toxicity of chemicals in animals (83). Vibration was found to accentuate the toxicity of manganese and to intensify the degenerative action of mercuric salts upon nerve elements. Similarly, morphological changes in internal organs of animals exposed to repeated doses of the organophosphate, trichlorofon, were more pronounced when animals were also subjected to prolonged noise stress.

II.5.4   Host Factors

It is well recognized that there may be considerable variation in the response of different individuals to a particular drug or chemical. This variation may be due to any one of many host factors which are "inherent factors related to the subject" (105). These factors include age, health status, sex, personal habits, nutritional status, diet and genetic status.
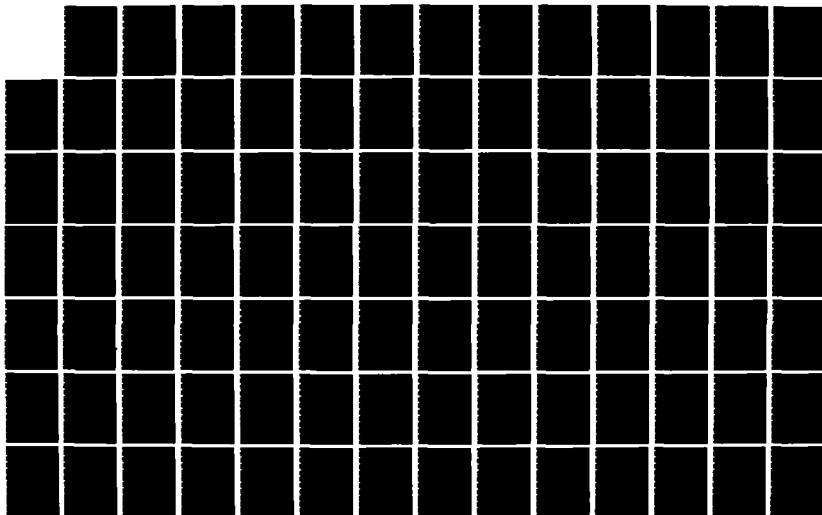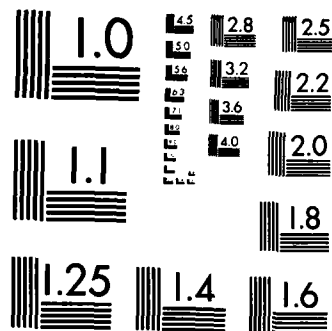
MICROCOPY RESOLUTION TEST CHART

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II.5.4.1 <u>Age</u>

Age, in itself, is not regarded as a significant factor in differences in response to foreign chemicals (106). However, it is generally accepted that, as an individual ages beyond 40 years, there is a gradual deterioration of physiological processes. Persons past 40 years of age tend to develop degenerative disease symptoms which are sometimes difficult to differentiate from symptoms resulting from exposure to certain chemicals (107). For example, symptoms such as weakness, fatigue, headache and malaise could result from physiological changes attributable to either natural processes or exposure to any of several solvents or other chemicals.

II.5.4.2 <u>Health Status</u>

As a general rule, exposure to foreign chemicals is better tolerated by individuals with healthy , well functioning physiolgoical systems. In these individuals, the uptake, distribution, metabolism and excretion of many chemicals, at low to moderate concentrations, are such that they are readily processed and eliminated with little or no consequences (108). In contrast, individuals with impaired respiratory, hepatic and/or renal functions who are exposed to the same chemicals may experience severe and possibly irreversible adverse effects.

The functional status of the liver and kidneys are particularly significant as a host factor because of the importance of these organs in tne biotranformation and excretion of foreign chemicals. Human patients with liver damage have an increased sensitivity to many drugs and chemicals as a consequence of an impaired detoxicating function of the liver. In patients with obstructive jaundice, hepatitis, cirrhosis and other liver diseases, glucuronide and sulfate conjugation of chemicals is impaired (83). This reduced ability of the diseased liver to metabolize a number of drugs and chemicals has been confirmed by experiments with animals. It has also been shown that, in animals with viral infections of the liver or various hepatic tumors, microsomal metabolism of foreign chemicals is impaired (83). Similarly, diseases or impairment of function of the kidney and other routes of excretion result in the reduced elimination of drugs and foreign chemicals

(83). The decreased elimination may cause high body concentrations of the compounds, and if threshold concentrations are reached, physiological alterations and toxic effects may occur.

Another possible consequence of a prexisting disease condition is that exposure to foreign chemicals may exacerbate this condition (109). For example, chemicals which act on the central nervous system may cause any preexisting alteration of the nervous system to proceed to a higher and more serious level of discomfort and injury.

II.5.4.3 Sex

Considerable data regarding sex differences in sensitivity to foreign chemicals have been obtained in experimental animal studies. However, the relevance of these data to humans has not been established. In these studies, male and female animals of the same strain and species usually exhibited only slight differences in susceptibility to toxic agents. There were, however, some notable exceptions (105). One of the most striking examples of a male-female difference is the nephrotoxic effect of chloroform in male mice of certain strains. Female mice of the same strains showed no effect from chloroform exposures that were lethal to male mice. This difference is apparently hormonal in nature since castration or the administration of estrogens reduced the effect in the male, and treatment with androgen increased susceptibility in the female. Sex differences in toxicity have also been observed in certain animal species with some of the organophosphate insecticides (Di-Syston, Guthion, EPN and parathion), many of the barbiturates, phenacetin, benzene, alcohol, and other chemicals. The most likely explanation for sex-related differences in toxicity is that sex hormones influence the enzymatic biotransformation of chemicals. Other hormonally dependent conditions may also influence the toxicity of various agents. For example, hyperthyroidism and hyperinsulinism may alter the susceptibility of animals, including man, to toxic agents. It has been suggested that many of these effects are due to stress-mediated hormonal mechanisms (105).

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II.5.4.4 Personal Habits

The lifestyle habits and activities of an individual, such as alcohol consumption, caffeine intake via coffee or tea and smoking of tobacco, will alter physiological and biochemical function (83). These effects, since they are commonplace, are often overlooked when considering the potential interactions of foreign chemicals. Nevertheless, these personal, and often different, chemical intakes do present potentials for chemical interactions with other foreign compounds in the occupational environment. One example is the interaction between xylene and ethanol demonstrated experimenally in the rat. In this study, inhalation of xylene, when coupled with ingestion of ethanol, produced severe liver damage while independent exposure to xylene or ethanol failed to do so (110).

II.5.4.5 Nutritional Status and Dietary Factors

The relationship of nutritional status and dietary factors to the toxicity of chemicals is reviewed in detail in the U.S. Department of Transportation Report entitled "Principles of Toxicological Interactions Associated with Multiple Chemical Exposures" (83). There are considerable animal data that demonstrate that nutrition and dietary factors exert a marked influence on the toxicity of certain foreign chemicals. Human data also exist that show that nutritional state and diet may influence the toxicity of chemicals, particularly drugs. Nutritional status affects the activities of the hepatic microsomal enzyme systems that metabolize foreign compounds. In studies in which male rats were starved, decreased rates of metabolism were observed in the hydroxylation of acetanilide, demethylation of meperidine and the metabolism of hexobarbital and other compounds. Rats also exhibited a diminished rate of drug metabolism, when they were maintained on a protein- or calcium-deficient diet. The protein-deficient diet resulted in an increased toxicity of acetylsalicylic acid, which was further increased by a deficiency of magnesium. Also, increased susceptibility to various pesticides (dieldrin, DDT, lindane, chlordane and others) has been observed in protein-deficient rats. In general, protein-deficient diets have been found to greatly reduce the level of cytochrome P-450, resulting in decreased activity of hepatic metabolizing enzymes and a diminished ability of the organism to metabolize

foreign compounds. Many other dietary factors, including vitamin E, ascorbic acid, calcium, iron and other trace elements, have been investigated for their effects on the toxicity of foreign chemicals and are reviewed in the Department of Transportation report (83). The relevance of the effects of these factors in experimental animals to humans has not been established.

II.5.4.6 Genetic Status

At one time all individuals who exhibited toxic responses upon exposure to subthreshold doses of chemicals or drugs were termed "hypersensitive" or "idiosyncratic" (83). However, it is now known that several genetically controlled drug and chemical relationships occur in humans. One example is the atypical or low serum cholinesterase level that occurs in certain individuals. Because of low levels of esterase enzyme, these individuals may exhibit prolongation of the muscular relaxation and apnea-producing effects of therapeutic doses of succinylcholine. Other examples of genetically controlled drug toxicity reactions are the production of polyneuritis in individuals who exhibit an impaired ability to acetylate izoniazid and the acute hemolytic anema that develops in individuals with a deficiency in the enzyme glucose-6-phosphate dehydrogenase (G6PD) when these individuals are exposed to aniline or aromatic nitro or amine derivatives. Individuals with the G6PD deficiency have also been found to be more susceptible to the hemolytic effects of other toxic agents (benzene, naphthalene, methylene blue, phenylhydrazine) and certain drugs (sulfaonamides, aspirin, primaquine, vitamin K). Other examples of genetically controlled differences in response to toxic agents can be found in various review articles and monographs (111, 112).

II.5.5 Biological Interactions

II.5.5.1 General Mechanisms

A fundamental toxicological principle is that the toxic effects produced by a chemical are proportional to the quantity of biologically active form of the chemical that is available for reaction with critical cellular reaction (target) sites (83). In accordance with this principle, toxicological interactions may involve any of three general mechanisms:

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1) the quantity of active toxicant may be altered by the presence (or past presence) of other chemical(s); 2) the binding or reaction of active toxicant with target sites may be altered by competition with other chemical(s) for these sites; and 3) the cellular responsiveness to a toxicant may be altered by previous or present reaction to other chemical(s).

The occurrence of a toxicological interaction depends on a number of factors. Obviously, the properties or intrinsic activities of the toxicant and interacting chemical(s) are a determining factor in whether a toxicological interaction can occur. Also, temporal relaticnships between exposure to the toxicant and exposure to other chemical(s) are a determinant. These relationships include the temporal order in which exposures to chemicals occur and the time interval between exposures to the chemicals. In the event an interaction does occur, the nature and extent of the interaction are also dependent on the properties of the toxicant and chemicals and the temporal relationships of exposure.

When exposures are simultaneous or proximate in time, the occurrence of a toxicological interaction will likely depend upon competition between toxicant and other chemical(s) for sites of absorption, biotransformation, reaction with target tissue and excretion. In these interactions, the concentration within the organism of each potentially interacting compound and the relative binding affinities and/or intrinsic activities of the chemicals are the most important factors. In contrast, when exposures are separated in time, the biological half-life of each chemical or its metabolites, the duration of binding to cellular reaction sites and the rate of injury repair may be more important factors than the relative binding affinities or intrinsic activities of the chemicals.

Another factor that can determine whether or not toxicological interactions will occur is the frequency of exposure. The frequency of exposure influences the accumulation of the body burden of the chemical(s), the accumulation of cellular injury and the opportunity for reversal of action or repair of injury.

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II.5.5.2 Sites and Mechanisms of Toxicological Interactions

Chemicals may interact with a toxicant at any phase of entry and passage of the toxicant through the body. Many interactions occur during absorption, distribution, metabolism and excretion of the toxicant or at the receptor sites. These interactions can alter the effects of toxicants by any of several mechanisms, including: direct effect on the toxicant; modification of its absorption; alteration of its distribution; modification of its action at receptor sites; modification of its biotransformation; and alteration of its excretion (83). Although it is recognized that toxicological interactions can occur by any of these mechanisms, specific data relevant to these inter- actions in the occupational environment are limited. Few dermal absorption or inhalation studies have been conducted with combinations of volatile chemi- cals. Most of the current knowledge of chemical interactions has been ob- tained from experimental studies of drugs in animals or from clinical drug studies in humans. For example, there is considerable information on how drugs such as cardiac stimulants, diuretics, hypertensive and hypotensive agents and other cardiovascular drugs affect the distribution of other drugs in the cardiovascular system. However, comparable information relevant to common occupational atmospheric contaminants is practically nonexistent. Similarly, there are considerable data on the effects of drugs on kidney function but little data exist regarding the interactive effects of many common industrial solvents on the excretion of other chemicals.

One mechanism of toxicological interactions which has received considerably more attention than others is the modification of biotransforma- tion of toxicants. Increased emphasis on this mechanism is probably due to the recognition that alterations in the metabolism of a given toxicant by other chemicals can lead to profound changes in the extent and/or duration of its biological effects. Although there is a vast amount of published litera- ture on the subject of biotransformation interactions, most of the data have been obtained in studies conducted under carefully controlled laboratory conditions. Unfortunately, few attempts have yet been made to determine whether the biotransformation interactions observed under laboratory condi- tions (acute dose, nonphysiological routes of exposure) occur in human popula- tions exposed to actual occupational conditions (low level, chronic, dermal or

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inhalation exposure) and, if they do, whether they constitute a toxic hazard.

There are a number of recent reviews of the subject of bio-transformation reactions (113, 114). The primary site for biotransformation of lipophilic foreign compounds is the hepatic cytochrome P-450-containing monooxygenase enzyme systems (80). Foreign chemicals may interact to either induce or inhibit these systems. Monooxygenase enzyme induction may lead to the reduced toxicity (detoxication) by enhancing the rate of metabolism of a *toxicant to inactive products.* Alternatively, enzyme induction may lead to an increase in toxicity (intoxication) through the enhanced rate of formation of active metabolites. In general, high levels of induction result from exposure to lipophilic materials which have prolonged biological half-lives (83). In recent years, increased attention has been directed at the *monooxygenase* system, and its induction by chemicals, in extrahepatic organs and tissues such as lung, skin and intestine. In some cases, these tissues may be of critical importance in biotransformation interactions resulting from inhalation or dermal exposures to chemical agents (83).

The monooxygenase system may also be inhibited by many different chemicals. The onset of inhibitory effects usually occurs quite rapidly after administration of the chemical inhibitor (83). Consequently, biotransformation interactions due to this *mechanism may occur more often than* those resulting from enzyme induction. Alteration of the biotransformation of a given toxicant may result in either decreased toxicity (detoxification) of the chemical by reducing the rate of formation of active metabolites or increased toxicity (intoxication) by reducing the rate of metabolism of a toxic chemical.

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III. EXPOSURE TO CHEMICALS DURING MARINE OPERATIONS AND EXPOSURE GUIDELINES

III.1   Introduction

Marine tank vessels transport a wide variety of chemical substances, some of which are also commonly encountered in the industrial environment. Exposure guidelines, which have been established for land-based industry, specify concentrations of atmospheric chemicals that are considered to be "safe" for exposure of individuals for prescribed durations or under prescribed conditions. Examples of these guidelines include the ACGIH Threshold Limit Values (TLVs), OSHA Permissible Exposure Limits (PELs), NIOSH Recommended Standards and Immediately Dangerous to Life or Health levels (IDLH).

The exposure conditions during marine operations are considerably different from those in the land-based industrial workplace. Consequently, these exposure guidelines for land-based industry may not be appropriate for evaluating typical exposures in the marine environment. Given this observation, the objectives of Chapter III are to

o   review existing exposure guidelines and their use in the conventional work schedule,

o   characterize potential exposures to chemicals during marine operations,

o   identify those features that require special consideration in assessing the potential toxicity and hazards of these exposures to the marine worker and

o   introduce the concept of adapting or adjusting existing exposure limits to reflect the maritime work/exposure environment.

III.2   Exposure Standards

III.2.1   ACGIH Threshold Limit Value

Threshold Limit Values (TLVs), which are established by the ACGIH, "refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly

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exposed without adverse effect" (1). Threshold limit values are based on the best available information from industrial experience, from experimental human and animal studies and, when possible, from all three sources. In the case of some chemicals, considerable information is available for establishing limit values. For other chemicals, TLVs are based on limited available data and may have to be revised when additional information becomes available. The ACGIH emphasized that these limit valued are recommendations and should be used as guidelines for control of health hazards. Thus, an exposure to a chemical in excess of a TLV does not necessarily mean that the individual will suffer toxic effects. Equally important is the understanding that, because of a wide variation in individual susceptibility, a few workers may experience discomfort from some chemicals at concentrations at or below the limit value, and a smaller percentage may be affected more seriously by aggravation of a pre-existing condition or by development of an occupational illness. Consequently, toxic effects will not always be produced by concentrations in excess of limit values and, conversely, concentrations below limit values may produce toxic effects in some individuals. However, whenever an exposure exceeds a TLV, a potential hazard is presumed to exist.

Three categories of Threshold Limit Values (TLVs) are specified by the ACGIH. These are 1) the Threshold Limit Value - Time-Weighted Average (TLV-TWA), 2) the Threshold Limit Value - Short-Term Exposure Limit (TLV STEL), and 3) the Threshold Limit Value - Ceiling (TLV-C). The TLV-TWA is defined by the ACGIH as "the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect (1). Excursions above the TLV-TWA are permitted provided they are compensated by equivalent excursions below the limit during the workday. The ACGIH points out that the amount by which threshold limits may be exceeded for short periods without injury to health depends upon a number of factors. These factors include the nature of the contaminant, its capability to produce acute poisoning at very high concentrations, the cumulative nature of effects, the frequency with which high concentrations occur and the duration of such periods. In the 1983-84 TLV listing, the ACGIH has included a recommendation that short-term exposures should not exceed three times the TLV-TWA value for more than a total of 30 minutes during a work day, provided the 8-hour TLV-TWA is not

exceeded and that, under no circumstances, should they exceed five times the TLV-TWA value.

In addition to the TLV-TWA, the ACGIH recommends TLV-STEL values for those substances with which toxic effects have been reported from high, short-term exposures in either humans or animals. The TLV-STEL is defined as "the concentration to which workers can be exposed continuously for a short period of time without suffering from 1) irritation, 2) chronic or irreversible tissue damage, or 3) narcosis of sufficient degree to increase the likelihood of accidental injury, impair self-rescue or materially reduce work efficiency, and provided that the daily TLV-TWA is not exceeded" (1). This limit value is a 15-minute time-weighted average exposure which should not be exceeded at any time during a work day, even if the eight-hour time-weighted average is within the TLV-TWA. Any exposure at the STEL concentration should not be longer than 15 minutes and should not be repeated more than four times a day, with at least 60 minutes intervening between successive exposures at the STEL. An averaging period other than 15 minutes may be recommended when warranted by observed biological effects. When an STEL value has been recommended for a chemical, this value takes precedence over the allowed excursion limit regardless of whether it is more or less stringent.

The third category of ACGIH Threshold Limit Values is the Threshold Limit Value - Ceiling (TLV-C), which is defined as the concentration that should not be exceeded even instantaneously. Ceiling limit values have been established by the ACGIH for a limited number of chemicals, primarily those which have predominantly fast-acting effects and for which the threshold limit is more appropriately based on these effects. Approximately 50 percent of the chemicals that have assigned ceiling limit values are transported in the marine industry.

Certain chemicals to which the ACGIH has assigned Threshold Limit Values have the capability of being absorbed in considerable quantities through the skin. The ACGIH identifies such chemicals in the TLV listing by the notation "Skin". This designation refers to the potential contribution to the overall exposure by the cutaneous route including mucous membranes and eye, either by airborne, or more particularly, by direct contact with the

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substance. Unless appropriate protective clothing is worn, it is possible that a sufficient quantity of chemical may be absorbed by the dermal route to cause toxic effects even when the inhalation exposure does not exceed a Threshold Limit Value. Therefore, the "Skin" notation is intended by the ACGIH to call attention to the need for appropriate measures to prevent cutaneous absorption so that the threshold limit is not invalidated.

Although the ACGIH establishes Threshold Limit Values for exposures to single chemicals, it also recognizes the possibility of exposure to mixtures of two or more substances. When two or more chemicals which act upon the same organ system are present, the ACGIH advocates that the combined effect of the chemicals should be given primary consideration and that the effects of the chemicals should be assumed to be additive. In such exposures, the Threshold Limit Value of the mixture is considered exceeded when the sum of the fractions (ratios of concentration to TLV of each chemical) exceeds unity, as shown in the following formula:

$$\frac{C_1}{T_1} + \frac{C_2}{T_2} + \frac{C_3}{T_3} + - - - \frac{C_n}{T_n} > 1$$

This formula is not applicable when the effects of the components of the mixture are not additive and are either independent, potentiating or synergistic.

The approach that was developed for toxicological evaluations of marine occupational exposures is based on the numerical values of the 1983-84 ACGIH TLVs.

III.2.2 OSHA Exposure Limits

The Occupational Safety and Health Act (OSH Act), which was passed in 1970, was designed to assure that no employee will suffer diminished health, functional capacity or life expectancy as a result of his work experience. Under this act, the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH)

were assigned the responsibility for ensuring, insofar as possible, that every working man and woman are provided with a safe and healthful working environment. Administration of OSHA is the responsibility of the Secretary of Labor, and he is authorized to set mandatory safety and health standards for atmospheric chemical contaminants as well as for work practices, equipment, protective devices and operational procedures in the occupational environment. The Act also calls for research in occupational safety and health to assist in the discovery of latent diseases, to establish the connection between diseases and the work environment and to study other health problems related to the occupational environment.

To initiate the establishment of exposure standards for chemicals in the occupational environment, OSHA adopted the ACGIH 1968 TLV-TWAs for chemical substances and designated them Permissible Exposure Limits (PELs). The PELs are defined as 8-hour, time-weighted average concentrations of chemicals which shall not be exceeded in any 8-hour work shift of a 40-hour work week. Ceiling limit values also were adopted for certain chemicals and represent the concentrations which shall at no time be exceeded in the work environment. However, in the case of a very limited number of chemicals of which benzene, carbon disulfide, carbon tetrachloride, ethylene dibromide, methyl chloride, trichloroethylene and tetrachloroethylene are examples, an "8-hour time weighted average," and "acceptable ceiling concentration" and an "acceptable maximum peak above the acceptable concentration for an 8-hour shift" are designated (2). The OSHA regulations state that "an employee's exposure to any of these chemicals shall not exceed at any time during an 8-hour shift the acceptable ceiling concentration limit, except for a time period, and up to a concentration not exceeding the maximum duration and concentration specified by the acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift" (2). In the case of mixtures of chemicals, OSHA has designated the same formula as that recommended by ACGIH to determine whether the exposure has exceeded the limit value. In addition to these exposure standards, OSHA and NIOSH have jointly established IDLH levels for many occupational chemicals. These "Immediately Dangerous to Life or Health" concentrations are defined as the maximum concentrations from which one could escape within 30 minutes without any escape-impairing symptoms or any irreversible health effects.

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In contrast to ACGIH TLVs which are guidelines and are revised yearly, OSHAs PELs are not changed without considerable effort. Changes to PELs contemplated by the Department of Labor require notices of intent and public hearings, and there is usually considerable debate over the justification and necessity of such changes. Changes to PEL values are even subject to reversal by court actions. Consequently, the OSHA PEL values are the same as the 1968 ACGIH TLV values, with revised values for only a few substances. However, although PEL values for several chemicals do not conform to current ACGIH TLV values, a general duty clause in OSHA regulations permits enforcement by OSHA of more stringent values.

III.2.3   Other Exposure Standards

The National Institute for Occupational Safety and Health (NIOSH) is the principal federal agency engaged in research to eliminate on-the-job hazards to the health and safety of this country's workers. The Institute was established under the provisions of the Occupational Safety and Health Act of 1970 within the Department of Health, Education and Welfare (HEW) which is now the Department of Health and Human Services (HHS). Administratively, NIOSH is located within HHS's Center for Disease Control of the Public Health Service. The Institute's main research laboratories are located in Cincinnati where studies are conducted on the effects of exposure to hazardous substances used in the workplace. Much of the research deals with specific hazards, such as asbestos and other fibers, beryllium, coal tar pitch volatiles, silica, noise and stress.

NIOSH is responsible for identifying occupational safety and health hazards and for recommending changes in the regulations that will reduce the hazards. In 1974, NIOSH and OSHA jointly began to develop a series of complete occupational health standards for substances with existing PELs. The project, designated the Standards Completion Program (SCP), resulted in a comprehensive review of available information on a number of these substances and documents containing technical information and recommendations for exposure limits. These technical documents are published by NIOSH as NIOSH Criteria Documents, NIOSH Current Intelligence Bulletins and NIOSH Recommended Standards. NIOSH also transmits its recommended exposure standards to the

Department of Labor, which then has the responsibility for their development, promulgation and enforcement.

It is important to differentiate between a NIOSH recommended standard and an OSHA regulatory limit value. In the case of occupational standards, Congress intended to separate risk assessment and risk judgement in the OSHA Act of 1970 (3). The function of NIOSH was intended to be the assessment of risk. Consequently, NIOSH considers only data relevant to the health effects of exposure to occupational chemicals in arriving at a recommended exposure standard. In contrast, the function of OSHA in the standards-setting process was intended to reflect the wishes of the body politic in judging the risk and, consequently, other factors besides health effects, such as economic impact and technological feasibility of the standard, must be considered. The process of risk judgement was intended by Congress to be an open one with the widest possible participation of all of our society. This judgement of risk acceptability is a controversial exercise in regulatory government and has often been challenged in the U.S. framework of government. In fact, it has been stated that OSHA operates on the assumption that every standard will be challenged in the courts (3).

One additional source of exposure limit value information is the manufacturers of chemicals. In the case of certain chemicals, particularly those for which limited toxicological data are available, the chemical manufacturer may publish chemical data bulletins which contain his recommendations for handling of the chemicals, protective clothing, other precautionary measures and maximum exposure concentrations.

The USCG has the authority to set occupational exposure limits for chemical substances and physical agents for the marine workers that are included within its jurisdiction. These exposure limits may include OSHA PELs, ACGIH TLVs or USCG-developed guidelines. The basis of this authority resides in-part from:

o 29 USCS, Section 653(b)(1). This section of the Code corresponds to Section 4(b)(1) of the OSHA Act of 1970 (Public Law 91-596) and states that the OSHA Act does not "apply to working conditions

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of employees with respect to which other Federal agencies, ..., exercise statutory authority to prescribe or enforce standards or regulations affecting occupational safety or health."

o   29 USCS, Section 653, Interpretive Note and Decision No. 19 which states that the OSHA Act does not apply to working conditions of seamen on vessels operating on the high seas.

o   "Authority to Prescribe and Enforce Standards or Regulations Affecting Occupational Safety and Health of Seaman Aboard Vessels Inspected and Certificated by the United States Coast Guard," USCG/OSHA Memorandum of Understanding, Federal Register, Vol. 48, No. 53, Page 11365, 17 March 1983. This MOU identifies the USCG as the dominant agency with respect to safety and health issues on inspected vessels.

III.3   Marine Chemicals

III.3.1   Classification by Code of Federal Regulations (CFR)

Hazardous bulk liquid cargos are regulated in marine transport by the United States Coast Guard under Title 46 of the Code of Federal Regulations (CFR). The regulations are documented under 46 CFR Parts 30-40, Subchapter D-Tank Vessels: Flammable and Combustible Cargos, and 46 CFR Parts 150-154, Subchapter O-Certain Bulk Dangerous Cargos. These regulations apply to substances carried in bulk by tankships and barges, which are considered hazardous and include liquids, liquefied gases, and compressed gases. More than 600 substances are regulated in marine transport under Subchapter D and Subchapter O.

III.3.2   Health Hazard Ratings and Exposure Guidelines

The bulk cargos in Subchapters D and O comprise a widely diverse group of chemicals which vary from substances such as edible vegetable oils to highly toxic carcinogens. The health hazard potential for chemical substances has been evaluated by a number of organizations including the National Fire Protection Association (NFPA), the National Academy of Science (NAS) and the American Conference of Industrial Hygienists (ACGIH). An expla-

nation of NFPA and NAS health hazard ratings is shown in Table III-1. Of the chemical substances included in Subchapters D and O, some 279 substances have an NFPA or NAS rating of 1 or greater and 201 substances have a rating of 2 or greater.

Many of the marine chemicals are also commonly encountered in the industrial environment where accidental and occupational exposures have yielded important toxicity data. These data as well as the results of re-search studies in animals have been used by the ACGIH to establish exposure guidelines to protect the safety and health of the industrial worker. The ACGIH annually publishes a listing of threshold limit values (TLVs) for toxic chemical substances in the industrial workplace atmosphere. These threshold limit values refer to airborne concentrations of chemicals to which workers may be repeatedly exposed day after day without adverse effect. Because the ACGIH limit values are specifically designed for occupational exposures and are updated annually, ACGIH standards are considered the best available guide in the control of occupational health hazards and are primarily used in this report. A listing of the subchapter D and Subchapter O substances for which ACGIH has adopted TLVs is presented in Table III-2. For each substance, the TWA and STEL values are shown, with the ACGIH "Skin" notation, when applicable.

III.3.3   Toxicity of Marine Chemicals

The more than 600 chemicals that are regulated in marine transport vary widely in chemical structure and physical and chemical proper-ties. This diversity in structure and properties is reflected in the wide range of toxicities exhibited by these chemicals, which have potential effects on almost every organ or system of the body. Specific examples of a limited number of these chemicals and the target organs affected by each are shown in Table III-3.

III.3.4   Carcinogens

Of the more than 600 cargos regulated under Subchapters D and O, eleven have been designated carcinogens by the ACGIH. These carcino-

TABLE III-1. NFPA AND NAS HEALTH HAZARD RATINGS

NFPA HAZARD RATINGS

Health Hazard	Definition
4	Materials which on very short exposure could cause death or major residual injury even though prompt medical treatment were given.
3	Materials which on short exposure could cause serious temporary or residual injury even though prompt medical treatment were given.
2	Materials which on intense or continued exposure could cause temporary incapacitation or possible residual injury unless prompt medical treatment is given.
1	Materials which on exposure would cause irritation but only minor residual injury even if no treatment is given.
0	Materials which on exposure under fire conditions would offer no hazard beyond that of ordinary combustible material.

NAS HAZARD RATINGS

Rating	Vapor Irritant	Liquid or Solid Irritant	Poisons
0	No effect	No effect	No effect
1	Slight effect	Causes skin smarting	Slightly toxic
2	Moderate irritation; temporary effect	First-degree burns, short exposure	Intermediate toxicity
3	Irritating; cannot be tolerated	Second-degree burns, few minutes' exposure	Moderately toxic
4	Severe effect; may do permanent injury	Second-degree and third-degree burns	Severely toxic

Table III-2. Subchapter D and Subchapter O
Substances with ACGIH TLV's*

Substance	CHRIS** Code	Skin Notation	TWA*** (ppm)	STEL (ppm)
Acetaldehyde	AAD		100	150
Acetic acid	AAC		10	15
Acetic anhydride	ACA		C5	--
Acetone	ACT		750	1000
Acetonitrile	ATN	Skin	40	60
Acrylamide	AAM	Skin	0.3 mg/m^3	0.6 mg/m^3
Acrylic acid	ACR		10	--
Acrylonitrile+	ACN	Skin	2	--
Allyl alcohol	ALA	Skin	2	4
Allyl chloride	ALC		1	2
Ammonia	AMA		25	35
n-Amyl acetate	AML		100	150
Aniline & homologues	ANL	Skin	2	5
Asphalt (petroleum) fumes	ASP		5 mg/m^3	10 mg/m^3
Benzene	BNZ		10	25
Benzyl chloride	BCL		1	--
1,3-Butadiene+	BDI		10	--
Butane	BUT		800	--
n-Butyl acetate	BCN		150	200
sec-Butyl acetate	BTA		200	250
Butyl acrylate	BAR		10	--
n-Butyl alcohol	BAN	Skin	C50	--
sec-Butyl alcohol	BAS		100	150
tert-Butyl alcohol	BAT		100	150
Butylamine	BTY	Skin	C5	--
p-tert-Butyltoluene	--		10	20
Camphor, synthetic	CPO		2	3
Caprolactam vapor	CLS		5	10
Carbon black	--		3.5 mg/m^3	7 mg/m^3
Carbon disulfide	CBB	Skin	10-	--
Carbon tetrachloride	CBT	Skin	5	20
Caustic Potash (Potassium hydroxide)	CPS		C2 mg/m^3	--
Caustic Soda (sodium hydroxide)	CSS		C2 mg/m^3	--
Chlorine	CLX		1	3
Chlorobenzene (Monochlorobenzene)	CRB		75	--
Chloroform	CRF		10	50

*   Based on 1983-84 ACGIH TLVs

** USCG Chemical Hazards Response Information System

*** C indicates ceiling limit

+   Intended change

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Table III-2. Subchapter D and Subchapter 0
Substances with ACGIH TLV's*
(Continued)

Substance	CHRIS** Code	Skin Notation	TWA*** (ppm)	STEL (ppm)
β -Chloroprene	CRP	Skin	10	--
o-Chlorotoluene	CTD	Skin	50	75
Cresol, all isomers	CRS	Skin	5	--
Crotonaldehyde	CTA		2	6
Cumene	CUM	Skin	50	75
Cyclohexane	CHX		300	375
Cyclohexanol	CHN		50	--
Cyclohexanone	CCH		25	100
Cyclohexylamine	CHA	Skin	10	--
Cyclopentadiene	--		75	150
Diacetone alcohol	DAA		50	75
Dibutyl phthalate	DPA		5 mg/m^3	10 mg/m^3
o-Dichlorobenzene	DBO		C50	--
p-Dichlorobenzene	DBP		75	110
Dichlorodifluoromethane	DCF		1000	1250
1,1-Dichloroethane	DCH		200	250
Dichloroethyl ether	DEE	Skin	5	10
Dichlorofluoromethane	--		10	--
Dichloromethane (Methylene chloride)	DCM		100	500
1,2-oichloropropane (Propylene dichloride)	DPP		75	110
Dichloropropene	DPS	Skin	1	10
2,2-Dichloropropionic Acid	DCN		1	--
Dichlorotetrafluorethane	DTE		1000	1250
Dicyclopentadiene	DPT		5	--
Diethanolamine	DEA		3	--
Diethylamine	DEN		10	25
Diethylene triamine	DET	Skin	1	--
Diethyl phthalate	DPH		5 mg/m^3	10 mg/m^3
Diisobutyl ketone	DIK		25	--
Diisopropylamine	DIA	Skin	5	--
Dimethyl acetamide	DAC	Skin	10	15
Dimethylamine	DMA		10	--
Dimethylformamide	DMF	Skin	10	20
Dimethylphthalate	DTL		5 mg/m^3	10 mg/m^3
Dioxane, tech. grade	DOX	Skin	25	100
Diphenyl (Biphenyl)	DIL		0.2	0.6

*   Based on 1983-84 ACGIH TLVs
**   USCG Chemical Hazards Response Information System
*** C indicates ceiling limit

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Table III-2. Subchapter D and Subchapter O
Substances with ACGIH TLV's*
(Continued)

Substance	CHRIS** Code	Skin Notation	TWA*** (ppm)	STEL (ppm)
Diphenylmethane diisocyanate (Methylene bisphenyl isocyanate)	DPM		C0.02	--
Dipropylene glycol methyl ether	--		100	150
Ethane	ETH		****	
Epichlorohydrin	EPC	Skin	2	5
2-Ethoxyethanol+	--	Skin	50	100
2-Ethoxyethyl acetate+	--	Skin	50	100
Ethyl acetate	ETA		400	--
Ethyl acrylate	EAC	Skin	5	25
Ethyl alcohol (ethanol)	EAL		1000	--
Ethylamine	EAM		10	--
Ethyl amyl ketone	--		25	--
Ethyl benzene	ETB		100	125
Ethyl chloride	ECL		1000	1250
Ethylene	ETL		****	--
Ethylene chlorohydrin	ECH	Skin	C1	--
Ethylenediamine	ECA		10	--
Ethylene dibromide	EDB	Skin	--	--
Ethylene dichloride	EDC		10	25
Ethylene glycol vapor	EGL		C50	--
Ethylene glycol methyl ether acetate+ (2-Methoxyethyl acetate)	--	Skin	25	35
Ethylene oxide+	EOX		10	--
Ethyl ether	EET		400	500
Ethylidene norbornene	ENB		C5	--
Formaldehyde+	FMS		C2	--
Formamide	FAM		20	30
Formic acid	FMA		5	--
Furfural	FFA	Skin	2	10
Furfuryl alcohol	FAL	Skin	10	15
Gasoline	GAT		300	500
Glutaraldehyde	GTA		C0.2	--
Heptane (n-Heptane)	HPT		400	500
Hexane (n-Hexane)	HXA		50	--
sec-Hexyl acetate	--		50	--
Hexylene glycol	HXG		C25	--
Hydrogen chloride	HDC		C5	--

* Based on 1983-84 ACGIH TLVs
** USCG Chemical Hazards Response Information System
*** C indicates ceiling limit
**** Simple asphyxiant
+ Intended change

Table III-2. Subchapter D and Subchapter O
Substances with ACGIH TLV's*
(Continued)

Substance	CHRIS** Code	Skin Notation	TWA*** (ppm)	STEL (ppm)
Hydrogen fluoride	HFX		3	6
Isoamyl acetate	IAT		100	125
Isobutyl acetate	IBA		150	187
Isobutyl alcohol	IAL		50	75
Isophorone	IPH		C5	--
Isophorone diisocyanate	IPD	Skin	0.01	--
Isopropyl acetate	IAC		250	310
Isopropyl alcohol	IPA		400	500
Isopropylamine	IPP		5	10
Isopropyl ether	IPE		250	310
Maleic anhydride	MLA		0.25	--
Mesityl oxide	MSO		15	25
Methacrylic acid	MAD		20	--
Methane	MTH		****	--
Methyl acetate	MTT		200	250
Methyl acetylene-propadiene mixture	MAP		1000	1250
Methyl acrylate	MAM	Skin	10	--
Methyl alcohol	MAL	Skin	200	250
Methylamine	MSZ		10	--
Methyl amyl alcohol (Methyl Isobutyl Carbinol)	MAA	Skin	25	40
Methyl n-amyl ketone	--		50	100
Methyl bromide	--	Skin	5	15
Methyl chloride	MTC		50	100
Methyl ethyl ketone	MEK		200	300
Methyl formate	MFM		100	150
Methyl isobutyl carbinol	MIC	Skin	25	40
Methyl isobutyl ketone	MIK		50	75
Methyl methacrylate	MMM		100	125
α-Methyl styrene	MSR		50	100
Morpholine	MPL	Skin	20	30
Naphthalene	NTM		10	15
Nitric acid	NAC		2	4
Nitrobenzene	NTB	Skin	1	2
1-Nitropropane	NPN		25	35
2-Nitropropane+	NPP		C25	
Nitrotoluene	NIT	Skin	2	--

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*   Based on 1983-84 ACGIH TLVs
**   USCG Chemical Hazards Response Information System
***   C indicates ceiling limit
**** Simple asphyxiant
+   Intended change

Table III-2. Subchapter D and Subchapter O
Substances with ACGIH TLV's*
(Continued)

Substance	CHRIS** Code	Skin Notation	TWA*** (ppm)	STEL (ppm)
Nonane	NAN		200	250
Octane	OAN		300	375
Pentane	PTA		600	750
Perchloroethylene+	PER		50	200
Phenol	PHN	Skin	5	10
Phosphoric acid	PAC		1 mg/m^3	3 mg/m^3
Phthalic anhydride	PAN		1	4
Propane	PRP		****	--
Propionic acid	PNA		10	15
n-Propyl acetate	PAT		200	250
Propyl alcohol	PAL	Skin	200	250
Propylene	PPL		****	--
Propylene glycol monomethyl ether	--		100	150
Propylene oxide	POX		20	--
Pyridine	PRD		5	10
Styrene, monomer	STY		50	100
Sulfur dioxide	SFD		2	5
Sulfuric acid	SFA		1 mg/m^3	--
1,1,2,2-Tetrachloroethane	TEC	Skin	1	5
Tetrahydrofuran	THF		200	250
Toluene	TOL		100	150
Toluene-2,4-diisocyanate	TDI		0 005	0.02
o-Toluidine+	TLI	Skin	2	--
1,2,4-Trichlorobenzene	TCG		C5	--
1,1,2-Trichloroethane	TCM	Skin	10	20
Trichloroethylene+	TCL		50	150
1,2,3-Trichloropropane	TCN		50	75
Triethylamine	TEN		10	15
Trimethyl benzene	--		25	35
Trimethyl phosphite	TPP		2	5
Triorthocrenyl phosphate	--		0 1 mg/m^3	0.3 mg/m^3
Turpentine	TPT		100	150
Valeraldehyde	VAL		50	--
Vinyl acetate	VAM		10	20
Vinyl chloride	VCM		5	--
Vinylidene chloride+	VCI		10	20
Vinyl toluene	VNT		50	100
Xylene (o-, m-, p-isomers)	XLO,M,P		100	150

* Based on 1983-84 ACGIH TLVs
** USCG Chemical Hazards Response Information System
*** C indicates ceiling limit
**** Simple asphyxiant
+ Intended change

TABLE III-3. TARGET ORGANS OF SELECTED MARINE CHEMICALS

Substance	Eyes	Ear	Respiratory Tract	CNS	PNS	Liver	Kidneys	Heart/ Cardiovascular	GI	Skin	Blood	Carcinogen
Acetone	X		X	X								
Acrylonitrile			X	X			X					X
Aniline											X	
Benzene	X		X	X							X	✓
n-Butyl Acetate	X		X	X								
n-Butyl Alcohol	X	X		X								
Carbon Disulfide				X				X				
Carbon Tetrachloride				X		X	X		X	X		X
Chloroform				X		X	X	X		X		X
Dichlorodifluoromethane								X				
Glutaraldehyde	X		X			X				X		
n-Heptane				X								
n-Hexane				X	X							
Methanol	X			X								
1-Nitropropane	X					X	X					
Nitrotoluene											X	
Perchloroethylene	X			X		X	X			X		
1,2,4-Trichlorobenzene	X		X	X		X	X					
1,1,1-Trichloroethane	X			X		X	X	X				
1,1,2-Trichloroethane	X			X		X	X					
Trichloroethylene			X	X		X	X	X	X			

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gens are presented in Table III-4. For each substance, the 8-hour Time Weighted Average (TWA) and the CHRIS code designation are provided. The ACGIH "Skin" notation has also been included for those substances so designated by ACGIH.

In addition to the substances listed in Table III-4, the carcinogenic potential of certain other substances and mixtures should be noted. Although not called out in the 1983-84 TLV document, the Subchapter O substance 1,1,2,2-tetrachloroethane is presently under consideration by ACGIH for inclusion as a carcinogen. Also, a number of mixtures which involve Table III-4 substances are regulated under Subchapter O. Examples of such regulated mixtures include:

o Benzene hydrocarbon mix (> or = 10% benzene)

o Benzene hydrocarbon mix (with acetylene, > or = 10% benzene)

o Benzene, Toluene, Xylene mix

o Butadiene, butylene mix (containing acetylene)

o Ethylene oxide, propylene oxide mix

o Nitropropane (1-, 2-, and mixtures)

o Nitropropane (60%), Nitromethane (40%) mix

In general practice, mixtures which include more than one percent of a highly toxic substance such as a carcinogen require precaution and special attention regarding airborne concentrations of the specific carcinogen.

III.4   Maritime Work Schedules and Exposure Potential

Maritime work schedules differ in many ways from the conventional work schedules of land-based industries. These differences range from annual to daily work schedules and include variations that reflect either the operational requirements or established practices on the vessel. The objectives of this section are to describe (1) the departure of the maritime work schedule from the conventional 8-hour day, 40-hour week and (2) the potential for occupational exposures during tank ship operations. The following discussion emphasizes the Deck Department because employees in this department are involved with cargo related operations.

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Table III-4. Regulated Substances That Have Been Designated Carcinogens By The ACGIH (1983-84)

Substance *	Skin Notation	CHRIS Code	TWA (ppm)
Acrylonitrile	Skin	ACN	2
Benzene		BNZ	10
Butadiene**		BDI	10
Carbon Tetrachloride	Skin	CBT	5
Chloroform		CRF	10
Ethylene Dibromide	Skin	EDB	--
Ethylene Oxide		EOX	1
Formaldehyde Solution		FMS	1
2-Nitropropane	Skin	NPP	10
o-Toluidine	Skin	TLI	2
Vinyl Chloride		VCM	5

* All of the indicated substances are regulated by the USCG under 46CFR, Subchapter O.
** A notice of intended change has been published for 1,3 Butadiene, which indicates intent to adopt carcinogen designation for this substance.

III.4.1 Annual Schedules

On the average, employees aboard U.S. flag tank ships work the equivalent of six months out of a calendar year. Within a 12-month period, the most common methods of distributing those six months are alternating periods of

o 90 days on - 90 days off
o 60 days on - 60 days off
o 30 days on - 30 days off

The number of days aboard a vessel may be extended if the ship is at sea at the end of a work period or if relief personnel are not available. In some cases, the employee may voluntarily request a work extension beyond the scheduled relief date. On some foreign flag vessels, the employee may contract for up to 12 months of continuous employment aboard the ship before receiving a vacation.

III.4.2 Traditional Daily Work Schedules and Variations

Historically, the daily maritime work schedule is based on naval tradition. The traditional schedule consists of alternating 4-hour watches separated by 8-hour rest periods. This schedule, which reduces to the equivalent of eight hours of work per day, applies seven days per week while the crew member is aboard the ship. As such, it differs from conventional land based schedules in that there are no rest periods that are analogous to weekends or the 16 hours that separate conventional work days.

A somewhat uncommon variation of the traditional schedule is the 6-hour on, 6-hour off routine. This routine may be used temporarily to accommodate a short-term increase in work load that results from operational considerations. For example, the modified schedule may be in effect on a parcel chemical tanker when several terminal dockings and cargo transfers are to occur within a short period of time. The traditional schedule is then re-instated as soon as practical.

The Deck Department includes both officers and unlicensed crew. The traditional work schedule tends to be followed by both of these groups during product loading and discharge. While the ship is underway (loaded or ballast condition), the officers and selected unlicensed personnel stand navigation watches that conform to the traditional schedule. When the ship is loaded and underway, the remainder of the unlicensed crew will normally work an 8-hour day during daylight hours. Maintenance and repair activities that are not related to the cargo tanks or cargo transfer systems are performed on this day work shift. Depending upon established operating procedures, for the ballast voyage, the remainder of the deck crew that are not standing navigation watch may perform tank cleaning activities solely on day work or on the traditional schedule. In the latter case, tank cleaning will proceed around the clock.

III.4.3 Extended Work Routines

The annual and traditional work schedules described above may be categorized as novel or unusual workshifts because they differ signifi-

cantly from conventional schedules. Within the framework of these unusual
workshifts, there are circumstances when a crew member may work continuously
through one or more regularly scheduled rest periods. The result is an ex-
tended work routine.

The duration of observed extended work routines ranged from
12 to 30 consecutive hours. Both licensed and unlicensed personnel were
involved. Specific examples of the work mix in an extended work period were
reported by Astleford (4). Basically, there are three situations that give
rise to extended work periods:

> o Defined responsibility - This situation involves
> the Chief Mate who is responsible for supervising
> all tank cleaning operations.

> o Overtime - On many chemical tankers, Deck Depart-
> ment personnel may average at least four hours
> overtime per day. Voluntary overtime activities
> include rust and paint chipping, painting and
> general equipment repair. Mandatory overtime
> arises for individuals who are off watch but are
> required on deck for vessel docking or undocking.
> As an example of documented overtime work, an able-
> bodied Seaman (A/B) accumulated 240 hours of over-
> time in a one-month pay period. For the A/B that
> stands an 0400-0800 and 1600-2000 navigation watch,
> the intervening eight hours may be occupied by
> overtime activities such as tank cleaning or deck
> maintenance. Weekend work is considered to be
> overtime whether the ship is in port or at sea.
> This example is equivalent to roughly 100 hours of
> work per 7-day week.

> o Shift swapping - In port, a crew member will work
> an extra watch so that others will have an oppor-
> tunity to go ashore.

The extended work routine, therefore, consists of a combina-
tion of the traditional work schedule and one or more of the above three
situations. The potential for an extended work period does not persist uni-
formly throughout a voyage. Qualitatively, the potential is greatest during:

> 1. The latter stages of cargo transfer through the
> first day after undocking;

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2. The day preceding docking through the initial stages of cargo transfer; and

3. The time following discharge when tanks are cleaned.

There are exceptions to these observations. For example, a Chief Mate may remain on duty and monitor the entire cargo transfer over a 2-day period. A Second Officer may work two regular cargo transfer watches plus an additional eight hours to assist a Port Relief officer who is not familiar with the vessel's tank layout or the cargo transfer systems.

III.4.4 Voyage Profile and Exposure Potential

An idealized voyage consists of four basic operations or legs.

o   Loading operation - Products to be transported are loaded aboard the ship.

o   Laden leg - The loaded ship sails to the discharge terminal.

o   Discharge operation - All products are transferred from the ship to the marine terminal.

o   Ballast leg - The empty ship takes on sea ballast for stability and sails back to the original loading terminal.

A typical round trip voyage from the Gulf Coast to the upper East Coast takes roughly 14 days. Gulf Coast/West Coast round trip voyages last approximately six weeks. On a fully utilized vessel, this cycle will be repeated continuously for two years. At the end of the 2-year period, the ship is temporarily removed from service for repairs and U.S. Coast Guard biennial inspection.

There are variations to the idealized voyage. The round trip voyage may include dockings at multiple loading and discharge terminals, but the basic voyage elements remain the same.

The potential for occupational exposures to chemical substances is not uniform throughout a voyage. The potential varies according to

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the voyage operations or leg and is influenced by the work activities and equipment that are involved. In this report, the term "chemical substance" refers primarily to chemical cargos and their vapors. The following discussion emphasizes cargo related exposures. However, exposure potential for non-cargo related sources will be identified where it is appropriate to provide an expanded perspective on marine operations.

The U.S. Coast Guard regulates in excess of 600 bulk liquid products. Parts of these regulations specify the minimum gauging requirements that are appropriate for a given chemical. The three types of gauging systems are listed below, along with an indication of the system's ability to release product vapors to the work environment.

System	Vapor Release Potential
Closed	None
Restricted	Minimal
Open	Maximum

Both product toxicity and vapor pressure are reflected in the specification of closed or restricted gauging systems. *The majority of the regulated products permit open gauging*, 56 of which have established exposure guidelines.

During product loading, the liquid level (ullage) is gauged periodically. A more extended gauging duration occurs at the end of loading when the tank is topped off by a crew member. In addition, the concentration of the vapor in the blanket above the liquid increases throughout loading to a saturated state at tank topoff. Therefore, the potential for occupational exposure to product vapors during loading is greatest for gauging:

        o   products that permit open gauging,

        o   tanks that are loaded to full capacity, and

        o   products that require closed or restricted
            systems but which are bypassed in favor of
            open gauging.

Unfortunately, the latter situation does occur for a combination of reasons that include:

o lack of confidence in the accuracy of closed
systems based on prior performance,

o concern for determining precise quantity of cargo
transferred,

o emphasis on spill prevention, and

o concern for loss of license if a spill occurs.

If restricted or closed gauging systems are used as intended during loading,
the potential for exposure to cargo vapors is greatly reduced.

Cargo is transferred to and from a ship via flexible hoses,
which must be connected to the ship's manifold prior to transfer and discon-
nected from the manifold after transfer is complete. During hose hook up and
disconnect, there is potential for short term inhalation exposure as well as
dermal contact with product liquids. Terminal transfer hoses and/or the
ship's manifold crossover piping may contain residual product. The removal of
flange blinds and hose/manifold couplings can release these residues. Dermal
and inhalation exposure can occur. Depending upon the marine terminal's
procedures, the transfer hoses may be connected and disconnected by dock
employees in which case the potential for crew exposure is minimal.

The drip tray beneath the manifold may contain a mix of
residual products from previous transfer dockings. These liquid mixtures can
evaporate and contribute to the exposure potential of the crew members who
connect/disconnect the hoses. At sea, tank washing slops, which contain a
mixture of chemical in water, may be discharged through an open manifold.
These slops may overflow the drip tray, which may contain pure chemical resi-
dues. The resulting overflow may flood the aft portion of the deck even
though the scuppers may be unplugged. In this case, there is a potential for
inhalation exposure as well as dermal exposure as a result of absorption of
liquids through shoe materials.

On the laden voyage when the ship is fully loaded, the
potential for product related exposures is minimal. Tank hatches and ullage
ports are closed and dogged down and may be sealed with tape or wax. Thus,
only intermittent, short duration vapor release through the vent line P/V

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valve may occur as a result of pressure buildup in the vapor space about the tank contents. These short-term vapor releases are rapidly diluted and disbursed by the ambient wind. The potential for non-cargo related exposures increases during the laden voyage. This leg of the voyage provides an opportunity for repair and maintenance activities that do not involve cargo tanks or deck piping/valving. Rust chipping and spray painting on the forepeak, for example, present the potential for exposure to noise, trace metal particulates in cured paints and primers as well as carrier solvents in the paints. On some ships, sandblasting is conducted while the ship is underway. In these cases, there is a potential for exposure to silica dust.

For many products, the minimum venting requirements specify that product vapors may be open vented at near deck level during loading. However, there is a substantial group of chemicals that have much stricter venting requirements. For these chemicals, the vapors must be vented at elevation, i.e. 4m or B/3 (one-third the breadth of the vessel) above the deck. These elevated vents may not be used because either (1) they are inoperable (lines plugged) in which case product vapors are discharged from the tank at near deck level through a cracked hatch or (2) they are bypassed to avoid back pressure so that loading can proceed at a higher rate. Deck work down wind of tanks that are venting product vapors at near deck level poses a potential exposure situation. The potential varies with the location of the work in relation to the source and the degree of dispersion and dilution of the vapor plume. Even when 4m or B/3 vents are used, certain operations and atmospheric conditions can result in potential exposures.

The ballast leg of the voyage poses a substantial potential for product vapor exposures. Ballasting into cargo tanks and tank cleaning/entry are the two operations that generate the potential.

Ballasting

After the cargo is discharged, the ship must be ballasted with sea water for stability on the return voyage. Ballast can be back loaded into dedicated ballast tanks or cargo tanks where the containment system forms an integral part of the vessel hull. The potential for vapor exposure occurs

during ballasting into integral cargo tanks. Depending on cargo volatility, the length of time between completion of product discharge and the start of ballasting may be sufficient to permit substantial evaporation of residual cargo into the empty tank. This evaporation increases the overall vapor concentration level in the tank such that the vapor levels that are discharged on deck during ballasting greatly exceed concentrations that have health significance and may even be totally within the flammable range throughout the ballasting. Thus, there is an enhanced potential for vapor exposure during ballast gauging throughout the ballasting operation. In addition, because a high concentration of vapor discharge persists throughout ballasting, there also exists the potential for exposure of crew members working down wind of cargo tanks that are being ballasted. During ballasting into cargo tanks as well as tank loading, the potential for vapor infiltration into crew quarters exists if wind conditions are correct. The above situations are rarely encountered on ships with dedicated ballast tanks because the cargo tanks are not ballasted.

Tank Cleaning/Entry

Tank cleaning and tank entry are two requirements of tankship operations. The degree and frequency with which these activities are conducted are a function of the products that are transported.

Tanks that carry pure chemicals are usually cleaned and entered on every voyage. This operation may be necessitated by an upcoming change in cargo grade, e.g. ketone to an ester, or to ensure the purity of the next product to the client even if the products are the same, e.g. ethanol to ethanol. The cleaning may or may not include a water wash followed by forced ventilation to dry the tanks, i.e. evaporate residues. Entry is accomplished to manually muck pump sumps and to sweep up debris that contains chemical residues.

Tanks that carry oils, gasolines and other petroleum products are cleaned less frequently because they are either dedicated to a given product or a change of grade is not critical to product purity, e.g. back loading a regular gasoline into an unleaded gasoline tank. These tanks are

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cleaned if the change in cargo grade is critical or if the tank is to be entered to inspect wall coating materials or to perform needed repairs to valves, pumps or gauging systems.

Cleaning and entering cargo tanks for U. S. Coast Guard biennial inspections are common to all inspected tank vessels.

During the washing operation, there is a potential for inhalation exposure of the deck crew to the vapors that are displaced from the tank due to the addition of wash water. An inhalation exposure potential for the deck crew also occurs during the gas freeing process when forced ventilation discharges vapor from the tank to the work environment.

There is a clearly defined potential for inhalation and dermal exposure during tank entry. In practice, the duration of the washing and gas freeing operations may be based on experience rather than adherence to a corporate tank cleaning procedure. The criteria for permitting tank entry may be based on experience and/or the sense of smell as opposed to the results of instrument tests of the atmosphere to ensure that concentrations are below levels that may be toxicologically significant. The use of combustible gas indicators may incorrectly infer the absence of toxic vapor concentrations. Consequently, tank entries do occur at vapor concentrations that may be considered toxicologically significant, although it should be stated that all confined space entries do not occur under these circumstances. When they do occur, there are times when respiratory or dermal protection is not always used.

Cleanup work in the tank poses the potential for dermal contact with the product that remains in any wash water residue or trapped in debris (rust, coating materials) on the tank bottom. The potential arises from the lack of protective clothing or the use of inappropriate apparel. Examples include personnel wearing shorts, open short sleeve shirts, slicker suits and leather gloves that are not impervious to chemicals.

III.4.5   Application of Limit Values and Adjustment Models
          to Marine Operations

          Marine operations and their potential for chemical exposures
of workers were reviewed in the preceding section of this report.   It is
apparent from that review that many of the exposures encountered by marine
workers are under conditions that differ considerably from those for which
existing exposure standards are intended. For example, TLV-TWA and PEL values
are established for workers exposed continuously to relatively low concentra-
tions of atmospheric chemicals during five eight-hour work days per week, with
intervening 16-hour periods without exposure. In establishing these values,
ACGIH and OSHA take into account that during these periods and the 48-hour
weekend, the body burden of many chemicals is eliminated by metabolism and/or
excretion of the chemicals. Also, excursions above the TWA-TLV and PEL are
allowed, but they must be controlled and maintained within the limits speci-
fied for concentrations, duration and frequency of exposure to comply with the
exposure standards. In non-maritime work environments, control and monitoring
of atmospheric concentrations of chemicals have become fairly routine so that
exposure excursions generally can be maintained within acceptable limits.

          In the marine environment, novel or unusual work schedules
with prolonged work shifts may not permit an adequate reduction of body burden
of chemicals, thus invalidating the application of TLV-TWA and PEL values. In
addition, exposure excursions may frequently exceed acceptable limits because
control and monitoring of concentrations, durations and frequency of exposure
are not readily accomplished during marine operations. This same limitation
of control and monitoring may result in marine worker exposures that exceed
other standards such as the TLV-STEL, TLV-C and OSHA ceiling values. Further-
more, these standards, as well as the 8-hour time-weighted averages, may not
be applicable to many of the exposures of marine workers to mixtures of chemi-
cals which have interactive effects.

          Existing exposure guidelines are based on a conventional
work schedule (8-hour work day, 40-hour work week) because the vast majority
of the land-based employees work this schedule, and measured exposures are
interpreted relative to those guidelines. Following the advent of unusual

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work schedules, e.g. four 10-hour work days/week), industrial hygienists became concerned about exposure interpretation and, more fundamentally, the applicability of these existing guidelines to the new schedules. These concerns are equally applicable to the maritime work schedule.

It is feasible but not practical to conduct the toxicity research that would generate exposure guidelines for all combinations of chemical substances and novel work schedules. Therefore, the approach that is being pursued by industrial hygienists and toxicologists is to mathematically modify or adjust existing limits that are based on a conventional work schedule to predict a new limit value for a novel work schedule. The concept of TLV adjustment involves calculating an exposure limit for the unusual work schedule that will result in a body burden that does not exceed the burden for a TLV level exposure during a conventional work schedule.

The concept of TLV adjustment for unusual work schedules is relatively new. Adjustment of existing standards to reflect the exposure conditions of marine operations has merit and is a promising approach to ensuring a safe work environment. Several methods for mathematically adjusting TLVs to unusual work schedules have been proposed. Five adjustment models including those that are based on body burden accumulation are presented and discussed in Appendix A. All of these models have limitations, and they will require additional development and eventually field validation before they can be applied to the exposure scenarios in marine operations.

The American Industrial Hygiene Association has a standing committee to give guidance on TLV adjustment. The efforts of this committee have just begun, with a long-term goal of developing formal adjustment guidelines. In the interim, the most prudent approach to maritime exposure interpretation appears to be to use the most current and conservative exposure limits for conventional schedules, and then to reduce these limits to a level considered safe for the unique exposure conditions of the marine environment. There may be an additional level of conservatism in this approach because maritime exposure profiles contain extended periods of no exposure.

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III.5 Factors Influencing Toxicity of Marine Chemicals

The major factors that may influence the toxicity of chemicals were reviewed in Section II.5. Some of these factors are of particular significance in the marine environment because of either the types of chemicals to which workers are exposed or the nature of these exposures. During marine operations, work schedules and activities result in types of exposures and conditions that differ considerably from those encountered in the conventional industrial workplace. For example, environmental conditions are not controlled in the marine environment. Consequently, the marine worker is exposed to wide ranges of temperature and humidity, with potential alterations of the toxicities of chemicals to which he is exposed. Fatigue of workers, as a result of extended work schedules, is also more likely in the marine than the industrial workplace, and this factor could alter the effect of a toxic chemical. In addition, exposures to mixtures of chemicals are more prevalent during marine activities. Thus, there is a much greater opportunity for the marine worker than the industrial worker to be exposed to chemicals with enhanced toxicities as a result of biological interactions. The following sections will review the major factors in the marine environment that may modify the toxicity of chemicals and need to be considered in an assessment of the potential hazards of exposures.

III.5.1 Dermal Absorption

Although the primary route of exposure of marine workers to chemicals is inhalation, significant dermal absorption is possible during certain operations. The potential for skin contact with liquid substances has been emphasized in previous sections of this report. Dermal contact with liquids is most likely to occur during manifold preparation and tank entry when personnel enter tanks without appropriate protective clothing. Even when instruments indicate that chemical vapors do not exceed recommended inhalation standards, it is possible that cutaneous absorption of liquid chemicals will invalidate the allowable standard. This possibility applies to a number of chemicals which, because of their physical and chemical properties, are absorbed in sufficient quantities to contribute significantly to the overall exposure of the individual.

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The ACGIH has recognized and emphasized the importance of dermal absorption to the potential toxicity of industrial chemicals. In the ACGIH listing of threshold limit values, a "Skin" notation is used to identify those chemicals for which the cutaneous route, including mucous membranes and eye, may contribute to the overall exposure of individuals. Significant quantities of these substances, either in vapor form or particularly by direct contact with the liquid phase, may be absorbed dermally and invalidate the threshold limit values, which are established for the inhalation route. Substances having a skin notation and a low limit value may present a severe problem at high airborne concentrations, particularly if a significant area of the skin is exposed for a long period of time. In such situations, toxic quantities of the chemicals may enter the body even though the respiratory system is protected. Consequently, the skin notation is used by the ACGIH as an attention-calling designation intended to suggest that appropriate measures be taken to prevent cutaneous absorption.

One of the chemicals that is readily absorbed through the skin in sufficient quantities to cause severe toxic effects is methanol. In fact, cases have been reported of death, blindness and other injury from methanol spilled on clothes or applied to the skin. One of the most serious cases involved 21 children who had clothes soaked in this alcohol applied to their abdomens and held in place by rubber pants (5). Signs of intoxication developed in one to 13 hours, with death occurring in 12 of the children. The rate of skin absorption of methanol by humans has been reported to be 0.192 $mg/cm^2/min$ (6). At this rate, immersion of a whole hand in the alcohol for two minutes would result in the absorption of 170 mg (0.2 mL) of methanol. This quantity is significant in view of the fact that blindness and death have been reported after ingestion of only 6 to 60 mL (7).

Many other chemicals are known to be readily absorbed through the skin, including aniline, carbon tetrachloride, phenol, acrylonitrile, n-butyl alcohol, carbon disulfide and nitrobenzene. Although few clinical cases of intoxication in industrial workers as a result of dermal absorption alone have been reported, the potential does exist for serious toxic effects from skin contact with these chemicals during specific vessel operations unless protective clothing is worn. One such chemical is aniline, the

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vapors of which have been found to be absorbed approximately equally by the skin and the lungs (8). Because of this potential for dermal entry, the ACGIH has recommended a TLV of 2 ppm and a STEL of 5 ppm for aniline, provided that absorption through the skin by contact with liquid is prevented (8). The potential for rapid absorption of carbon tetrachloride by the skin is well illustrated by the experiments of Stewart and Dodd (9), in which human volunteers immersed one thumb in the chemical for 30 minutes. Concentrations of the solvent in exhaled breath were in the range of 0.69-5.23 mg/liter. For comparison, inhalation of 10-11 ppm for 5 hours yielded breath concentrations of approximately 6 mg/liter 25 minutes after the end of the exposure (10). Thus, it is evident that, in the case of several chemicals, dermal absorption may contribute significantly to the overall exposure of an individual and result in adverse effects even when the atmospheric concentration does not exceed allowable standards.

III.5.2 Environmental Factors

One of the most important environmental factors that may influence the toxicity of chemicals is the temperature. Most toxicity studies of the effects of this factor have been with drugs rather than industrial chemicals. However, the few studies of chemicals have shown that this factor may alter the toxicity of a number of marine chemicals, including benzene, trichloroethylene, toluene and 1,1,1-trichloroethane. In one animal study, elevated temperature was reported to enhance the toxicity of 1,1,1-trichloroethane (11). In a more recent study, the acute toxicity of benzene and trichloroethylene in mice increased markedly at a low temperature of 8°C, as well as at a high temperature of 38°C (12). The acute toxicity of toluene was only enhanced at a high temperature of 38°C. Although the results of these animal studies demonstrate that the toxicity of chemicals may be altered by environmental temperature, the relevance of these findings to humans is not known. Temperature extremes do cause stress in humans and, therefore, it is possible that the activity of metabolizing enzymes and the metabolism of chemicals in humans will be altered under these conditions. However, it should also be noted that, in these studies, high doses were administered in order to cause death, administration was by routes other than inhalation and only mice were used. Additional research is needed to determine the effects of temperature

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on the sublethal toxicity of chemicals and in more than one species. Also, the mechanism of any altered toxicity observed as a result of temperature needs to be elucidated.

The effects of temperature on chemically-induced carcinogenesis have also been investigated in animals. In a study by Weisbrode and Weiss (13), the time required for tumor development and death as a result of benzo[a]pyrene (BP) administration to mice was decreased when the animals were kept in a cool environment and increased in a warm environment. The results indicated that the warm environment diminished the preneoplastic proliferative response of skin to BP and subsequently delayed the onset and reduced the incidence of squamous carcinomas induced by high and low doses, respectively, of the chemical. Although BP is not a marine chemical, the results of this study are significant since a number of marine chemicals are carcinogens. However, at this time, the relevance of the results of this study to potential effects of temperature on exposure of marine workers to carcinogenic substances is unknown.

III.5.3 Host Factors

Diet has been shown to alter the toxicity of chemicals, some of which are commonly transported in the marine industry. For example, food deprivation for one day accelerated the metabolism of a variety of hydrocarbons and altered the susceptibility of animals to various hepatotoxic agents, including carbon tetrachloride, chloroform and 1,1-dichloroethylene (vinylidene chloride) (14, 15, 16, 17). Dietary modifications of protein intake were also found to have a marked effect on carbon tetrachloride hepatotoxicity. High-protein diets resulted in severe liver damage in rats by accelerating carbon tetrachloride metabolism to highly reactive metabolites, whereas a low-protein diet decelerated metabolism of the chemical and protected animals from the damage (18, 19, 20). Diets rich in carbohydrates had the opposite effect of protein diets and protected animals against carbon tetrachloride-induced hepatic injury (21). More recently, Nakajima and others (22) investigated the effects of dietary carbohydrate on the metabolism of eight volatile hydrocarbons, i.e., benzene, ,toluene, styrene, chloroform, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloruethylene and trichloro-

ethylene. These investigators reported that a carbohydrate-deficient diet enhanced the metabolism of these chemicals and that carbon tetrachloride hepatotoxicity was directly correlated with carbohydrate intake. They concluded that carbohydrate, rather than protein or fat, regulates the metabolism of these chemicals and thereby may alter their toxicity. Other host factors such as age, health status, genetic status and personal habits were reviewed in Section II.5 and generally apply to the toxicity of all drugs and chemicals foreign to the body. All of these factors may influence a marine worker's response and tolerance to a chemical but insufficient data are available to predict to what degree the toxicity of the chemical will be altered. Perhaps the most important of these factors is the health status of the worker, particularly with respect to liver and kidney functions, since many of the marine chemicals are hepatotoxic and nephrotoxic agents. The toxic effects of such chemicals may be much more serious in workers in whom these organs have decreased function. Also, workers with enzyme deficiencies that make them more susceptible to certain marine chemicals need to be identified.

III.5.4 Biological Interactions

Of those factors capable of modifying the toxicity of chemicals in the marine environment, the potential for biological interactions among chemicals is undoubtedly the most important. This factor assumes this degree of importance primarily because of the nature of work activities during marine operations. Inherent in many of these work activities are the opportunities for simultaneous exposures of personnel to a number of different chemicals or to sequential exposures to different chemicals. As a consequence of such exposures, biological interactions may occur and result in marked alterations of the toxicity of these chemicals to the marine worker.

One of the chemicals that has received considerable attention in the area of biological interactions is ethyl alcohol. This chemical has been reported to potentiate the toxicity of several industrial solvents both in animals and in humans. This is in contrast to most other chemicals that have been observed to be capable of interactive effects only in animal studies. Moon (23) reported that ethyl alcohol enhanced the hepatotoxicity and nephrotoxicity of carbon tetrachloride in humans. This toxicological

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interaction of ethanol has also been observed with carbon tetrachloride and chloroform in studies with animals (24, 25, 26). Potentiating effects have also been observed in humans exposed to trichloroethylene who ingested ethanol (27). The effects have been described as "degreaser's flush," in reference to the vasodilatation of blood vessels in the face and neck. Recent clinical studies have shown that ethyl alcohol may also interact with m-xylene, causing dizziness and nausea (28). Ingestion of the alcohol four hours prior to xylene inhalation appeared to inhibit the metabolism of xylene, as indicated by 1.5- to 2-fold increases in xylene blood concentrations and decreased excretion of metabolite. Chronic administration of ethanol also may result in enhanced toxicity of other chemicals. For example, Radke (29) found that a low oral dose of ethanol administered chronically to rats receiving vinyl chloride by inhalation caused a more rapid and greater incidence of tumors.

A number of chemicals have been investigated for interactive effects with other chemicals because of severe peripheral neuropathies observed in acute and chronic inhalers of glues and paint thinners in industry and in drug abusers. Those chemicals, which are of importance in marine transport, include n-hexane, methyl n-butyl ketone (2-hexanone) and toluene. The neuropathies have been observed in humans and in experimental animals exposed to these solvents or various metabolites of some of these chemicals. There is evidence that the effects of these neurotoxicants may be potentiated by other common solvents, resulting in the earlier development of more severe neuropathies. For example, Altenkirch and others (30) reported that methyl ethyl ketone is capable of synergizing the neurotoxicity of methyl n-butyl ketone and n-hexane. Dyro (31) investigated the interactive effects of methyl ethyl ketone with toluene and acetone. In patients with neuropathies who had been exposed to methyl ethyl ketone and toluene, this investigator suggested that the ketone enhanced the neurotoxic effects of toluene. Although the concentrations of the two chemicals were estimated, it is significant that the concentrations of both chemicals were not excessive and generally below the threshold limit values. In other workers exposed simultaneously to methyl ethyl ketone and acetone, Dyro found that the combination caused more neurological damage than either solvent acting independently. Other reports of industrial toxicity cases have involved the presence of methyl ethyl ketone in a mixture with other solvents, including 2-nitropropane and an unsaturated

ketone impurity (32, 33). Ketones or chemicals which are metabolized to ketones have also been reported to potentiate the effects of other chemicals, including several aliphatic acetates and various haloalkanes in animal studies (34, 35, 36).

These examples of biological interactions are only a fraction of those reported in the literature, most of which have been identified as a result of animal experimentation. The significance of these studies is that they demonstrate that simultaneous exposures to chemicals or even exposure to one chemical prior to exposure to another may result in enhanced toxicities of chemicals. It is not possible to predict from such studies the threshold concentrations of the chemicals or durations of exposure necessary for this potentiation to occur in humans. The ACGIH does recommend a formula for evaluating the additive effects of chemicals which act upon the same organ system, but this formula is not applicable to the potentiating effects or synergistic actions of chemicals. Consequently, it is not possible to establish allowable concentrations for these chemicals in many simultaneous or sequential exposures of the marine worker. However, it is important to be aware that an exposure to a nontoxic concentration of a chemical may actually produce toxic effects when biologically interacting chemicals are also present.

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IV. TOXICOLOGICAL ASSESSMENTS OF MEASURED EXPOSURE DATA

IV.1 Introduction

The marine industry and responsible government agencies have recognized that occupational exposures to chemical vapors are inherent in maritime work activities. The United States Coast Guard has formulated and implemented a multi-element program to characterize the work/exposure environment and identify potentially hazardous safety and health operations. As part of this program, the project "Investigation of the Hazards Posed by Chemical Vapors Released in Marine Operations - Phase II" was conducted by the Southwest Research Institute. In this project, occupational exposures of marine workers were monitored in order to provide a direct indication of exposure levels and to identify those work activities in which potentially significant exposures to chemical vapors may occur. More than 200 exposure samples were collected for various work activities including single and multi-event exposures during tank entry, tank gauging and on-deck work activities (1). The purpose of this section is to provide a toxicological assessment of these measured occupational exposure data.

It should be emphasized that the assessments were made on a body of data that was available at a given point of time during this project. Since that point in time, the body of exposure data has been expanded considerably as a result of another USCG research and development project (2). These latter data are not included in the assessments discussed in this report.

IV.2 Assessment Criteria and Rationale

In the previous section, existing exposure guidelines were reviewed and the limitations in their application to marine operations were discussed. Because of differences in exposures between the marine and the industrial environments, these guidelines may not be directly applicable to some of the exposures encountered by marine workers. However, these guidelines are based on a comprehensive review of available toxicity data and can be applied and interpreted in a conservative manner to identify toxicological

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hazards in the marine environment. This was followed in selecting criteria for assessing the exposure data collected during occupational monitoring of marine workers.

A two-tiered approach, based on current ACGIH Threshold Limit Values (TLVs) (3), was adopted for toxicological assessment of the occupational exposure data. The ACGIH TLVs were used instead of OSHA Personal Exposure Limits (PELs) because the TLVs are reviewed and revised annually in an attempt to keep them in agreement with currently available information. On the other hand, the PELs have not been revised for a number of years. The TLV values published for 1983-84 were used throughout the assessments presented in this document.

In the Tier I evaluations, the exposure data were screened in order to identify those exposures that are of toxicological significance and require further evaluation. An exposure was considered toxicologically significant if it met the criterion for an occupational exposure for medical monitoring purposes. An exposure was designated an occupational exposure for medical monitoring purposes if the concentration of the chemical(s) equals or exceeds 50 percent of the TLV-TWA for the chemical or mixture of chemicals. This criterion is in accordance with guidelines promulgated in the USCG Medical Manual, COMDTINST M6000.1, Change No. 27, dated June 28, 1984, which states that, unless otherwise specified, a person engaged in a designated occupation is considered occupationally exposed for medical monitoring purposes if the concentration in the work environment "is equal to or more than 50 percent of the time weighted average of the applicable workplace standard for at least three days per calendar quarter" (4). In applying this criterion to the exposure data, the assumption was made that the individual encountered comparable concentrations in his work activities for at least three days per calendar quarter. This is a realistic assumption for U. S. flag chemical tankers that routinely transport a relatively fixed group of chemicals. For vessels that make two-week round trip voyages, there would be six voyage opportunities to meet the exposure criteria.

During some work activities that were monitored, workers were exposed to a number of chemicals simultaneously. During other activities,

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sequential exposures to a number of chemicals occurred, sometimes without sufficient time elapsing between the exposures to allow complete metabolism or elimination of the chemicals. If the chemicals in the simultaneous or sequential exposures act upon the same organ system, the ACGIH additive formula was used to determine whether the exposure equals or exceeds 50 percent of the TLV of the mixture, unless there is evidence that the chemicals act independently. In the latter situation, the concentration of each chemical was compared with the TLVs for each chemical to determine whether any component of the mixture equals or exceeds 50 percent of the respective TLV.

In the Tier I screening process, a number of exposures were identified as meeting the Tier I criterion and requiring further assessment. Those that did not meet this criterion were not considered toxicologically significant and required no further assessment.

In the Tier II evaluations, in-depth toxicological assessments were made of those exposures that meet the Tier I criterion. These assessments were based primarily on human toxicity data obtained from accidental and industrial exposures, but relevant experimental animal data were also used in the case of some chemicals, when human data were not available or limited. In addition, factors unique to the marine environment were also considered in applying these human and animal data to the measured exposures. However, it should be emphasized that quantitative relationships between experimental animal data and human toxicity have not been established for many chemicals encountered in marine operations. Consequently, it is often not possible to predict from animal data what concentrations of chemicals will produce effects in humans or to what extent factors, such as temperature, age, dietary conditions, biological interactions, will modify the toxicity of these chemicals in humans. Furthermore, even when human toxicity data are available, the conditions under which the marine exposures occur often differ considerably from those in the industrial environment with the result that the prediction of toxic effects from these data may be speculative.

In summary, the two-tiered method developed and applied to assess the toxicological significance of occupational exposures in the marine environment consists of the following elements of logic:

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Exposure assessment is based on the current ACGIH Threshold Limit Values.

A medical monitoring response level is defined as one-half of the TLV-TWA for individual chemicals or vapor mixtures regardless of exposure duration.

Exposure concentrations less than the medical monitoring response level are not considered to be toxicologically significant.

Exposures equal to or greater than the medical monitoring response level are considered to be toxicologically significant and are designated occupational exposures for medical monitoring purposes. The precedent for this criterion is contained in the USCG Medical Manual (COMDTINST M6000.1, Change No. 27, dated 28 June 1984.

The Tier I evaluation identifies those exposures which are less than the medical monitoring response level and thus require no further assessment and those exposures which are equal to or greater than the medical monitoring response level and thus require further assessment.

The Tier II evaluation consists of an in-depth toxicological assessment of those exposures equal to or greater than the medical monitoring response level.

IV.3 Toxicological Assessments

IV.3.1 Single Event Exposures

Single event exposures are characterized as exposures which result during work activities meeting one or more of the following criteria:

The work activity is relatively short in duration;

The work activity was suspected apriori of having a high probability of elevated exposure levels;

The work activity was confined to a single work station during the exposure period.

Tier I Evaluations

The measured exposure data for 19 single event exposure sequences during marine operations (1) are summarized in Table IV-1. It is

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evident from the data in this table that the majority of these single event exposures involved two activities, namely confined space entry and tank top-off. Each single event exposure is identified by a sequence number and involved the exposure of one or more personnel usually to one chemical but, in some cases, to more than one. In some sequences, one individual was exposed to one chemical and another individual was exposed to a different chemical or to more than one chemical. Therefore, a personnel designator (Pers. Des.) letter is included in the table to designate the sample numbers that correspond to each person and, thus, the chemical(s) to which each was exposed in the sequence. The length of time to which each person was exposed is shown by the sampling duration. The exposure concentration represents the measured average concentration of the chemical during the sampling period; it is probable that excursions above and below this concentration occurred during the sampling period. Each of the 19 single event exposure sequences was evaluated to determine whether the exposure meets the criterion of a medical monitoring response level, i.e., equals or exceeds 50 percent of the TLV-TWA value for the chemical. The American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs) for 1983-1984 were used for these evaluations. Of the 19 exposure sequences, 14 do not meet the criterion for this response level, are not considered toxicologically significant and do not require further discussion. Five exposure sequences (Nos. 1, 4, 5, 7 and 17) do meet the criterion of a medical monitoring response level and are considered of toxicological significance. An in-depth toxicological assessment of each of these exposure sequences is presented in the following Tier II evaluations.

Tier II Evaluations

In Sequence No. 1, entry of three crewmen into a tank containing residual methyl isobutyl ketone (MIK) resulted in exposures of 111, 47 or 85 ppm of MIK for approximately 20 minutes. All of these concentrations exceed 50 percent of the TLV-TWA (50 ppm) for MIK and meet the criterion of a medical monitoring response level; two concentrations (111, 85 ppm) exceed the TLV-STEL value of 75 ppm. These concentrations represent the measured average

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TABLE IV-1. SINGLE EVENT EXPOSURE SUMMARY*

Seq-uence No.	Pers. Des.	Sample No.	Chemical	Chem. Abr.	Sampling Duration (min.)	Exposure Conc. (ppm)	TLV-TWA (ppm)	TLV-STEL (ppm)	TLV-C (ppm)	Work Activity	Toxicological Significance**/Comments
1	A	PS-1	Methyl isobutyl Ketone	MIK	20.48	111	50	75	--	Tank Entry	OVA Mean Concentration 67 (47-96) ppm
	B	PS-2	Methyl isobutyl ketone	MIK	20.90	47	50	75	--	Tank Entry	MMRL (A, B, C)
	C	PS-3	Methyl isobutyl Ketone	MIK	21.45	85	50	75	--	Tank Entry	
	A	PS-4	Toluene	TOL	37.28	230	100	150	--	Tank Entry	OVA Mean Concentration 240 (200-273) ppm
	B	PS-5	Toluene	TOL	36.07	197	100	150	--	Tank Entry	
	C	PS-6	Toluene	TOL	38.38	229	100	150	--	Tank Entry	
2	D	UCC-110	n-Butyl Alcohol (Skin)	BAN	26	21	--	--	50	Tank Entry	NTS
	E	UCC-100	n-Butyl Alcohol (")	BAN	27	6	--	--	50	Tank Entry	
	F	UCC-101	Acetone	ACT	29	20	750	1000	--	Tank Entry	
3	G	UCC-105	n-Butyl Alcohol (Skin)	BAN	34	10	--	--	50	Tank Entry	NTS
	H	UCC-102	n-Butyl Alcohol (")	BAN	34	15	--	--	50	Tank Entry	
4	I	--	Ethylene Dichloride	EDC	85	>700	10	15	--	Tank Entry	MMRL
5	J	DM-2	Ethylene Dichloride	EDC	7.0	138	10	15	--	Tank Entry	MMRL
	J	DM-10	Trichloroethylene	TCL	8.7	29	50	150	--	Tank Entry	
	J	DM-3	Trichloro-oethane	TCE	5.0	45	350	450	--	Tank Entry	
6	K	SB-30	Benzene	BNZ	82	3.8	10	25	--	Tank Entry	NTS (BNZ in Gasoline)
7	L	PE-1	Toluene	TOL	35.37	199	100	150	--	Tank Top-Off (O.G.)	MMRL (L)
	L		Hexane	HXA	35.37	2	50	--	--	Adjacent Tank	
	M	PE-5	Hexane	HXA	34.93	944	50	--	--	Tank Top-Off (O.G.)	MMRL (M)
	N	PE-4	Hexane	HXA	40.75	66	50	--	--	Tank Top Off Assist.	
8	O	UCC-104	Ethyl Alcohol	EAL	21	112	1000	--	--	Tank Top Off (O.G.)	NTS
	O		Acetone	ACT	21	78	750	1000	--	Adjacent Tank	

* Data from Table V.1 on pages 230 and 231 of Reference 1.

** MMRL = Exposure meets criterion of medical monitoring response level.

NTS = Not of toxicological significance because exposure concentration is below medical monitoring response level.

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TABLE IV-1. SINGLE EVENT EXPOSURE SUMMARY*

(Continued)

Sequence No.	Pers. Des.	Sample No.	Chemical	Chem. Abr.	Sampling Duration (min.)	Exposure Conc. (ppm)	TLV-TWA (ppm)	TLV-STEL (ppm)	TLC-C (ppm)	Work Activity	Toxicological Significance**/Comments
9	P	UCC-103	n-Butyl Alcohol (Skin)	BAN	49.5	1.2	--	--	50	Deckside; Tank Washing	NTS
	P	UCC-106	n-Butyl Alcohol (")	BAN	50.5	.0	--	--	50	Deckside; Tank Washing	
10	Q	SB-10	Benzene	BNZ	6	N.D.	10	25	--	Open Ullage Ports and Gauging Tubes	NTS (BNZ in Gasoline)
	Q	SB-11	Benzene	BNZ	9	N.D.	10	25	--		
11	R	VF-7	Benzene	BNZ	22	0.5	10	25	--	Muck Pumproom Bilge	NTS (BNZ in Gasoline)
	R	VF-8	Benzene	BNZ	22	0.8	10	25	--	Muck Pumproom Bilge	
12	S	VF-10	Methyl ethyl ketone	MEK	13	1.2	200	300	--	Ullage Port Sampling	NTS
	S		o,m,p-xylene	XLO,M,P	13	0.1	100	150	--	Ullage Port Sampling	
13	T	VF-100	Benzene	BNZ	17	N.D.	10	25	--	Water Ballast Tank Entry	NTS
14	U	VF-102	Ethyl Alcohol	EAL	84	>67	1000	--	--	EAL Tank Entry to Access Adjacent EPC Tank	NTS (Possible EAL Breakthrough)
	U		Epichlorohydrin (skin)	EPC	84	0.4	2	5	--		
15	V	VF-103	Ethyl Alcohol	EAL	30	>239	1000	--	--	Tank Entry, Mucking	NTS (Possible EAL Breakthrough)
16	W	VF-11	Benzene	BNZ	144	N.D.	10	25	--	Ballast Tank Entry	NTS
	X	VF-13	Benzene	BNZ	165	N.D.	10	25	--	Ballast Tank Entry	
17	Y	107	Chloroform	CRF	15	31.7	10	50	--	Tank Entry	MMRL (Y, Z, Al)
	Y	108	Chloroform	CRF	15	22.4	10	50	--	"	
	Y	109	Chloroform	CRF	10	14.0	10	50	--	"	
	Z	524	Chloroform	CRF	15	26.9	10	50	--	"	
	Z	525	Chloroform	CRF	15	17.1	10	50	--	Tank Entry	
	7	526	Chloroform	CRF	10	10.6	10	50	--	"	
	Al	110	Chloroform	CRF	15	30.4	10	50	--	"	
	Al	112	Chloroform	CKF	26	28.6	10	50	--	"	
18	Al	113	o,m,p-Xylene (skin)	XLO,M,P	6	2.74	100	150	--	Tank Entry	NTS by itself
19	A2	504	m-Xylene (skin)	XLM	5	4.2	100	150	--	Tank Entry	NTS
	A3	505	m-Xylene (skin)	XLM	4	<0.86	100	150	--	Tank Entry	

* Data from Table V.1 on pages 230 and 231 of Reference 1.

** MMRL = Exposure meets criterion of medical monitoring response level.

NTS = Not of toxicological significance because exposure concentration is below medical monitoring response level.

concentrations for the sampling period; therefore, it is likely that excursions in concentrations were considerably higher than these averages. Following this exposure to MIK, these same personnel entered a tank containing residual tolune (TOL) and were exposed to average concentrations of 230, 197 or 229 ppm for 36 to 38 minutes. These concentrations exceed the TLV-TWA (100 ppm) and meet the criterion of a medical monitoring response level; the concentrations also exceed the TLV-STEL (150 ppm) for TOL. It is likely that excursions considerably greater than these averages occurred during the exposure period.

Methyl isobutyl ketone (MIK) is an irritant and is also capable of producing central nervous system depression and narcosis at relatively high concentrations, i.e., approximately 1000 ppm (5). Silverman et al. (6) reported that 12 persons exposed to MIK for 15-minute periods found that 200 ppm had an objectionable odor and definitely caused eye irritation. In other studies, it was reported that 5-minute exposures to concentrations of 200 to 400-ppm MIK produced eye irritation in 50 percent of the exposed volunteers and 400 ppm produced nasal irritation in 50 percent of the volunteers (5). However, symptoms have been reported in workers exposed to even lower concentrations of MIK. In a study by Armeli et al. (7), the measured MIK concentration during 15-30 minute operation of a centrifuge was 100-105 ppm, with vapor concentrations of 50 ppm elsewhere in the room. A few of the workers complained of gastrointestinal and central nervous system effects. Elkins (7) also reported symptoms in workers exposed to concentrations of MIK comparable to those encountered during tank entry. Some of the workers, who were exposed to 100 ppm MIK in the waterproofing of boots, complained of headache and nausea, and others complained only of respiratory irritation. Although industrial exposures are generally of longer duration than the tank entry sequence, the data indicate that exposures during entry of tanks containing residual MIK may produce irritant effects in the eyes and respiratory tracts of crew members as well as other symptoms such as headache, nausea, dizziness and gastrointestinal disturbances. In addition, impaired judgement may be produced by MIK at concentrations which are not presently known and narcosis would result at high concentrations (8). All of these symptoms would be exacerbated by prolonged or repeated exposures.

Although the most likely route of exposure of maritime personnel to methyl isobutyl ketone (MIK) is inhalation of the vapors during tank entry or gauging activities, exposure by skin and/or eye contact is also possible. Skin contact should be avoided because the defatting property of MIK produces a dermatitis. Also, direct contact of the eyes with this chemical produces a painful irritation.

Toluene (TOL) also is an irritant and vapors may produce conjunctival and respiratory tract irritation. The chemical has defatting properties similar to those of MIK and repeated or prolonged skin contact may cause drying, fissuring and dermatitis. Contact of the eye with liquid toluene has been reported to produce transient disturbances of the eyes, consisting of corneal damage and conjunctival irritation (9). At high vapor concentrations, TOL is a central nervous system depressant and narcotic and may produce paresthesia, disturbances of vision, dizziness and nausea, narcosis and collapse (10).

The toxic effects that may be anticipated from exposures to the concentrations of TOL that were measured during tank entry are primarily eye and throat irritation and, possibly, central nervous system effects, including headache, lassitude, fatigue, exhilaration and slowed reflexes. These symptoms have been reported in humans exposed to comparable concentrations, although for longer periods of time (human short exposure data are limited). For example, Carpenter et al. (11) reported the following responses in human subjects exposed to various concentrations of TOL for seven to eight hours: at 200 ppm, transitory, mild throat irritation and slight exhilaration; at 400 ppm, mild eye irritation, lacrimation, nausea and hilarity; at 600 ppm, lassitude, hilarity, verbosity and boisterousness; and at 800 ppm, metallic taste, transitory headache, extreme lassitude, dimmed vision and inebriation. More pronounced effects were reported in a study by von Oettingen and others (12, 13) involving controlled 8-hour exposures of subjects to purified TOL. Symptoms observed at 200-ppm TOL included mild fatigue, muscular weakness, impaired coordination, moderate dilation of the pupils and paresthesias of the skin. These same symptoms were intensified at 300 ppm whereas mental confusion was also noted as a result of exposure to 400 ppm. The narcotic effects of toluene became more severe at higher expo-

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sure levels. *The findings of von Oettingen are supported by those of Wilson* (14) who reported acute exposure effects of TOL ranged from dizziness at 0-200 ppm to mild incoordination at 500-1500 ppm. The latter investigator was of the opinion that exposures to TOL should not exceed 200 ppm. Gamberale and Hultengren (15) also exposed human volunteers to TOL, at concentrations of 100, 300, 500 and 714 ppm. They reported concentration-related increases in reaction time and decreases in perceptual speed beginning at 300 ppm.

Other human data and, particularly, experimental animal data suggest that toluene (TOL) may exert toxic effects in addition to irritation and CNS depression. However, it should be noted that these effects generally occurred after longer exposures and/or at higher concentrations than those measured during tank entry. Matsushita et al. (16) reported that workers exposed to 60 to 100 ppm daily for three to four months had an increased incidence of tendon reflex abnormality and muscular weakness. Syrovadko (17) reported increased disturbances in the peripheral nervous system of workers exposed to what was described as "high" doses of TOL. Suzuki (18) exposed five volunteers to 200 ppm TOL for six hours and compared various electro-physiological recordings to five unexposed controls. Electrodermal and finger plethysmograph records, respiration and electroencephalograms were not affected but heart rate increased as a function of exposure time. Also, reversible pathological changes in the liver and kidney have been reported in clinical case reports of humans who were either accidentally or intentionally exposed to high levels of TOL and/or for long periods (19, 20, 21). In animal studies also, reversible changes in the kidney and liver have been reported; however, in a review of the effects of TOL on the liver and kidney, Benignus (22) stated that human and animal studies were not consistent in their find-ings of pathology. This investigator pointed out that most human clinical studies were conducted on essentially healthy and unimpaired subjects and that permanent damage to the liver and kidneys might be produced in more sensitive subjects (the young, the old, those with impaired function), particularly when other stressors of these organs are present. A number of other diverse effects of TOL have been reported in animal studies, including changes in blood components, dopamine turnover in the brain, operant performance, learn-ing ability, activity and behavior, sleep and electrocardiographic activity (22). However, it is not known if TOL produces similar effects in humans and at what concentrations and durations of exposure these effects would occur.

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Animal studies also have demonstrated that the toxicity of toluene (TOL) may be modified by certain host factors. These studies have shown that lethality induced by administration of or exposure to TOL is a function of species and age and possibly of gender, strain and involvement of pregnancy (22). It has also been shown in animal studies that the concomitant exposure to certain other chemicals can alter the rate of metabolism of TOL and alter its toxicity. For example, pretreatment of rats with phenobarbital, which induces hydroxylating enzymes in the liver, reduced TOL-induced sleeping time and increased the excretion rate of hippuric acid (23). Sato and Nakajima (24) showed that benzene and toluene slowed the elimination of each other at high dose levels, but at lower levels in both rats and man (25 and 100 ppm, respectively) no significant interactions occurred. Similar results were obtained for toluene and trichloroethylene, also only at high levels (25). Also, Kocsis et al. (26) reported that the simultaneous administration of dimethyl sulfoxide reduced the lethal dose of TOL in animals by a factor of 10. In summary, these studies have shown that TOL can produce a wide variety of toxic effects and can interact with other chemicals in animals. Although the relevance of these findings to humans has not been established, the possibility that these same effects and interactions could occur in humans under certain exposure conditions should be recognized in the medical monitoring of exposed workers.

Thus, exposures of personnel to methyl isobutyl ketone (MIK) or toluene (TOL) at the concentrations measured during tank entry may produce irritation of the eyes and respiratory tract and CNS depressant effects, with additional effects possible in the case of TOL. The CNS depressant effects (impaired judgement, slowed reflexes and fatigue) are potentially hazardous becasue they render the worker more prone to accidents, with possible serious consequences. Moreover, the sequential exposure to MIK and TOL constitutes an increased hazard because both chemicals have the potential to depress the CNS. Additive, or even synergistic, interaction between the two chemicals is possible, unless metabolism and/or elimination of MIK from the body occurs prior to exposure to TOL. These interactions could result in irritant and/or CNS depressant effects that are much more severe than would be anticipated from the measured concentration of either chemical.

In Sequence Nos. 4 and 5, crewmen were exposed during tank entry to ethylene dichloride (EDC) at concentrations of at least 700 ppm for 85 minutes and of 138 ppm for 7 minutes, respectively. Both of these concentrations are considerably greater than the TLV-TWA (10 ppm) and TLV-STEL (15 ppm) of this chemical and meet the criterion of a medical monitoring response level. In addition, the concentration in Sequence No. 4 is not much lower than the IDLH Level of 1000 ppm established by OSHA for EDC.

Ethylene dichloride (EDC) is considered one of the more toxic of the chlorinated hydrocarbons. The chemical produces a wide array of effects, and it is difficult to identify primary target organs or systems. Inhalation exposure has been reported to adversely affect the circulatory, respiratory and nervous systems and the liver, kidneys, skin and mucous membranes. Many clinical cases of acute exposure were reviewed in the NIOSH criteria document for a recommended standard for EDC (27). Workers acutely poisoned by occupational exposure to EDC developed symptoms indicative of CNS depression, including headache, weakness, dizziness, feelings of drunkeness and sometimes unconsciousness, followed by respiratory and circulatory failure and death. In some cases, workers who were not overcome during exposure became unconscious later. Other symptoms reported following acute exposure to EDC are conjunctival irritation, cyanosis, nausea and vomiting. Evidence of liver and kidney damage has been observed, as indicated by increased serum bilirubin, decreased blood glucose, tender and palpable liver and the presence of albumin, blood cells, and hyaline and granular casts in the urine. In fatal cases, autopsies have revealed hyperemia and hemorrhagic lesions in the stomach, intestines, heart, brain, lungs, liver and kidneys. In many of the cases of acute exposure in which fatalities occurred, a wide range of susceptibility of individuals to EDC was evident. For example, 15 cases of poisoning were reported in Italy following the fumigation of a warehouse with EDC (27). Four workers had been involved in the fumigation during the afternoon and the other 11 persons lived nearby. That night, most of the individuals developed signs and symptoms that included malaise, nausea, vomiting, headache, anorexia, tiredness, asthenia, epigastric pain and mild hepatomegaly. One of the four workers became seriously ill and was hospitalized with tachycardia, oliguria and decreased renal and hepatic function, but recovered. One person who lived near the warehouse died on the eighth day after exposure.

Autopsy findings included meningeal hemorrhaging, hyperemia in the cephalic parenchymal cortex, congested and edematous lungs, clots in the heart and a thickening of the myocardium, congestion of the liver and spleen, renal hyperemia, and centrilobular liver necrosis. This incident illustrates not only the variability in susceptibility to EDC among individuals but also the wide range of organs that may be affected by this chemical.

Despite the many clinical reports of acute intoxication by ethylene dichloride (EDC) inhalation, usually little information was provided as to the EDC concentrations involved in the exposures. Consequently, data that would enable the correlation of acute exposure concentrations and durations with toxic effects produced are very limited. In addition, apparently large individual differences in susceptibility to EDC toxicity complicate estimation of the threshold effect concentration for both acute and chronic exposures. In two Russian reports of several year's experience with EDC, it was stated that acute effects from inhalation of EDC occurred following exposure to 75 to 125 ppm, with symptoms that included general weakness, headache, dizziness, vomiting and irritation of the skin and mucous membranes (27). When workers experienced these signs and symptoms two or more times in a period of two to three weeks, fatalities resulted. The duration of exposure at which these symptoms occurred was not provided in the reports. In another study in which exposure conditions were monitored, two industrial workers were exposed to EDC at concentrations of about 120 ppm or higher for short periods (2 to 15 minutes) from one to ten times daily (27). The workers developed sensory and motor problems during six to nine months of exposure, with symptoms (anorexia, epigastric pains, fatigue, irritability and nervousness) first appearing after three weeks of exposure. Experimental human studies also have been conducted, but only at very low concentration and for short durations (27). In these studies, a 30-second exposure of four subjects to 1.5 ppm EDC caused a temporary stenosis of the blood vessels in all of the subjects. Changes in the depth of beathing were also reported after short exposures to low concentrations of EDC vapors.

Chronic occupational exposures also have resulted in numerous reported cases of ethylene dichloride (EDC) intoxication (27). Repeated exposures have produced neurological changes, anorexia, nausea, vomiting,

epigastric pain, irritation of mucous membranes and liver and kidney dysfunction. Although fatalities have occurred less frequently with chronic exposure than with acute exposure, chronic exposures have resulted in toxic effects which progressed to death in some cases. Definitive studies that would allow delineation of safe exposure levels in the industrial workplace are nonexistent. However, there are reports of adverse effects on the cardiovascular system, nervous system, liver and bile ducts in industrial environments in which peak concentrations of EDC exceeded 20 or 25 ppm (27). Because of these reports, the ACGIH has recommended a TLV-TWA value of 10 ppm and a TLV-STEL value of 15 ppm for EDC. The National Institute of Occupational Safety and Health (NIOSH), however, recommended a TLV-TWA of 5 ppm because of a report by Kozik (27) of adverse nervous system and liver effects in workers exposed to time-weighted average concentrations of only 10 to 15 ppm.

Experimental exposures of animals to ethylene dichloride (EDC) have produced toxic effects and pathological changes similar to those observed in humans. At high concentrations, CNS depressant effects were evident after relatvely short exposures. Thus, in a study by Sayers et al. (28), guinea pigs exposed to 4000 and 4500 ppm EDC became unconscious in 30 minutes. In the same study, a monkey exposed to 4500 ppm was unable to maintain itself on the perch of the cage after 10 minutes. In rabbits, rats and mice that expired after exposure to 3000 ppm EDC, Heppel et al. (29) reported pulmonary congestion and hemorrhage, generalized visceral congestion, hepatic necrosis and slight fatty degeneration of the renal tubular epithelium. Guinea pigs exposed to the same concentration developed focal necrosis of the adrenal cortex and fatty degeneration of the myocardium. Repeated 7-hour exposures at 1500 ppm resulted in hemorrhage in the lungs, stomach, intestines and adrenals, fatty degeneration of the myocardium and congestion in the liver and intestines of rats, guinea pigs, rabbits and dogs. In a study by Spencer et al. (30) in which a variety of animals were exposed to 400 ppm EDC for seven hours per day, one of two exposed monkeys died after eight exposures and the other died after 12 exposures.

In view of the serious toxic effects reported for acute human exposures to ethylene dichloride (EDC), the exposures encountered during tank entry in Sequence Nos. 4 and 5 must be regarded as extremely hazardous. This

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is particularly true of the exposure to at least 700 ppm EDC for 85 minutes. In fact, it is surprising that the crewman did not complain of adverse effects, even though there is a wide range of susceptibility to EDC. It is possible that symptoms would have occurred in a more sensitive worker. These exposures are particularly hazardous in marine operations that require sequential exposures to other CNS depressants following entry into an EDC tank. Possible delayed effects of EDC together with potentiation of CNS depression by many other toxicants which have CNS activity could result in a very hazardous exposure sequence.

In Sequence No. 7, one crewman (Pers. Des. L) was exposed to 199 ppm of toluene (TOL) for approximately 35 minutes during top-off by open gauging of a TOL tank. The individual was also exposed to 2 ppm of hexane (HXA) from an adjacent tank. The concentration of TOL exceeds the TLV-TWA (100 ppm) and TLV-STEL (150 ppm) values for TOL and the limit value for the mixture of the two chemicals and meets the criterion of a medical monitoring response level.

The toxicity of toluene (TOL) was reviewed previously in the toxicological assessment of Sequence No. 1. Since the TOL concentration and duration of crew member exposure in Sequence No. 7 are similar to those measured in Sequence No. 1, anticipated symptoms from the two TOL exposures should be comparable. These symptoms are primarily eye and throat irritation and, possibly, central nervous system effects such as headache, lassitude, fatigue, exhilaration and slowed reflexes. In Sequence No. 7, the crewman was simultaneously exposed to hexane (HXA) vapors from an adjacent tank. Although HXA also is an irritant and acts on the CNS, the concentration of vapors was very low (2 ppm), and the contribution of HXA to the combined exposure would most likely be minimal and toxicologically insignificant. In this same sequence, another crew member (Pers. Des. M) was exposed to 944 ppm of HXA for approximately 35 minutes during tank top-off. This concentration is considerably greater than the TLV-TWA (50 ppm) of this chemical and meets the criterion of a medical monitoring response level. However, HXA is not considered a highly toxic chemical, except for potential neurotoxic effects as a result of chronic exposures. Although these effects were recognized in the late 1960's, their seriousness was not appreciated until 1973 when an outbreak of

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peripheral neuropathy occurred at a fabrics-coating plant in Ohio (31). Consequently, the TLV-TWA for this chemical was reduced from 500 ppm to 100 ppm and eventually to 50 ppm in 1980.

Acute exposure data in the literature indicate that symptoms from the exposure to 944 ppm of hexane (HXA) in Sequence No. 7 might include eye and upper respiratory tract irritation, headache and nausea. Eye and throat irritation were reported following human exposure to 880 ppm HXA for 15 minutes (10). Other reports differ as to the threshold effect concentration of HXA. For example, according to Patty and Yant (7), no effects resulted in man after an exposure to 2000 ppm for 10 minutes, but 5000 ppm caused dizziness and a sense of giddiness. In another report, eye and throat discomfort, headache, and less commonly, nausea were experienced by some of the human subjects exposed to 1500 ppm for 10 minutes (32). In a study by Veulemans et al. (33), human volunteers were exposed to lower concentrations of 100 or 200 ppm for four hours. Although this study was designed to measure respiratory uptake and elimination, there was no mention by the investigators of any symptoms resulting from these exposures. Human exposures for several minutes to 500 ppm HXA have also been reported to be without adverse effects (34). Animal studies also have shown that high concentrations of HXA are required to produce CNS depressent effects. A five-minute exposure of mice to various concentrations of HXA revealed: at 8000 ppm, no anesthesia; at 16,000 ppm, light anesthesia; at 32,000 ppm, deep anesthesia; and at 64,000 ppm, respiratory arrest (35, 36).

Peripheral neuropathy is the major toxic effect of chronic exposure to hexane (HXA). Little information has been reported on other organ or tissue pathology resulting from chronic HXA exposure. The possibility of liver damage from chronic HXA exposure is suggested by the work of Bühlen et al. (37) which related HXA inhalation to hepatic liver accumulation in rats. Also, DiVicenzo and Krasavage (38) found that HXA produced an increase in serum ornithine-carbamyl transferase activity in guinea pigs. Couri and Milks (39) suggested that, although hepatotoxicity is not the most prominent toxic effect of HXA, it should be considered in the clinical evaluation of occupationally exposed workers.

In Sequence No. 17, crew members were exposed during in-tank activities to chloroform (CRF) vapors for a total of approximately 40 minutes. Measured average concentrations in samples collected from these crewman ranged from 10.6 to 31.7 ppm. These concentrations exceed the TLV-TWA of 10 ppm for this chemical and meet the criterion of a medical monitoring response level. Inhalation of high concentrations of CRF may result in narcosis and anesthesia, resulting from depression of the central nervous system (40). Responses reported from exposure to concentrations below anesthetic levels are typically inebriation and excitation passing into narcosis. In addition, vomiting and gastrointestinal upset may be observed. Exposure to high concentrations also may result in cardiac sensitization to adrenalin and to similar compounds as well as in liver and kidney injury. In cases of more chronic or repeated exposure to CRF, liver injury is more typical and resembles the effect of carbon tetrachloride. Although injury to the kidney is not as common as that to the liver, it may be observed from either acute or chronic exposure. However, symptoms from the acute exposures that occurred in this sequence would not be anticipated on the basis of toxic effects reported at various concentrations in the scientific literature. For example, it has been reported that man can tolerate an exposure of 389 ppm CRF for 30 minutes without any ill effects, but that an exposure to 1024 ppm will result in dizziness, intracranial pressure and nausea after 7 minutes (40). Vomiting and a sensation of fainting have resulted from exposure to approximately 4100 ppm, and anesthesia has been produced at concentrations in the range of 10,000 ppm. Thus, these data indicate that man can tolerate considerably higher acute exposures than those measured in this sequence before toxic effects result.

Although chloroform (CRF) has been used in industrial operations for many years, there are relatively few clinical reports of toxic effects produced in man as a result of chronic or intermittent inhalation of CRF vapors. Challen and others (40) reported that workers exposed in industry to concentrations varying between 77 and 237 ppm, with some higher peak concentrations, exhibited severe symptoms (lassitude, digestive disturbances, mental dullness). Another group of workers exposed to concentrations from 21 to 72 ppm showed less severe symptoms. Although not specifically stated, these industrial exposures were probably daily 8-hour exposures. Liver func-

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tion tests performed on both groups of workers were negative, but the investigators pointed out the insensitivity of the tests performed and stated that there may have been mild injury in these cases. In another study, Bomski et al. (7) reported enlarged livers in 25 percent of the workers handling CRF in a chemical plant, with exposures ranging from 10 to 200 ppm for one to four years.

Although it is unlikely that symptoms would result from single exposures to chloroform (CRF) vapor concentrations in the range of those that were measured during tank entries, the exposures in this sequence are of particular toxicological concern because of the suspected carcinogenic potential of CRF. Chloroform has been classified as a suspect carcinogen in man by the ACGIH and, accordingly, Threshold Limit Values for the chemical were lowered to 10 ppm (TLV-TWA) and 50 ppm (TLV-STEL). In 1976, because of the suspected carcinogenic potential of this chemical, NIOSH recommended that the TLV-TWA value be further decreased to 2 ppm (7). In addition to its suspected carcinogenicity, CRF has also been reported to be teratogenic and highly embryotoxic in animal studies (7). In view of the suspected carcinogenicity of CRF, the potential for exposures in excess of limit values during tank entry and the possibility of subsequent exposures to other suspected carcinogens, medical monitoring of all workers exposed to CRF and efforts to eliminate exposures to CRF are warranted.

IV.3.2 Single Shift/Operations Oriented Exposures

Exposures in this category include those wich result from work activities associated with operations that are generally somewhat longer than those producing single event exposures. Examples of these work activities are tank sampling and top-off during barge loading, tank cleaning operations, repetitive tank gauging during loading, periodic open tank gauging and tank top-off.

Tier I Evaluations

The measured occupational exposure data for 12 single shift or operations oriented exposure sequences (1) are summarized in Table IV-2. Some

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of the sequences resulted in exposure of crew members to single chemicals whereas others involved exposures to mixtures of several chemical vapors. Each sequence was evaluated to determine whether the concentration or concentrations of mixtures of chemicals equal or exceed 50 percent of the TLV-TWA value for the chemical or mixture and thus meet the criterion of a medical monitoring response level. Of these 12 sequences, the concentrations of chemicals in eight sequences are below 50 percent of the TLV-TWA values and are not considered of toxicological significance. These sequences are not discussed further. In the other four sequences (Sequence Nos. 1, 2, 4 and 8), the concentrations of chemicals equal or exceed 50 percent of the TLV-TWA values and meet the criterion of a medical monitoring respone level. In-depth toxicological evaluations of these sequences are presented in the following Tier II evaluations.

Tier II Evaluations

In Sequence No. 1, one of the workers received a series of three short (12 to 58 minutes) exposures to methyl alcohol (MAL) vapors during the loading of a methanol barge. During one of the exposures the average concentration of MAL was 249 ppm which exceeds the TLV-TWA (200 ppm) of this chemicals and meets the criterion of a medical monitoring response level.

Numerous cases of methyl alcohol (MAL) poisoning have been reported in the literature, with most resulting from ingestion of the alcohol. The most characteristic symptoms following oral intake are various visual distubances and metabolic acidosis. There is a controversy over whether formaldehyde or formic acid, both of which are metabolites of MAL, is responsible for these effects. In industrial operations, inhalation is the most likely route of exposure. This is also the most likely route in the marine environment, although absorption of toxic quantities through the skin particularly during tank entry is a possibility.

The widespread use of methyl alcohol (MAL) in a variety of manufacturing processes has resulted in the inhalation exposure of numerous workers. Industrial injuries and fatalities have been reported from the inhalation of high concentrations but, surprisingly, the incidence of indus-

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TABLE IV-2. SINGLE SHIFT OR OPERATIONS ORIENTED EXPOSURES*

Sequence No.	Pers. Des.	Sample No.	Chemical	Chem. Abr.	Sampling Duration (min.)	Exposure Conc. (ppm)	TLV-TWA (ppm)	TLV-STEL (ppm)	TLV-C (ppm)	Work Activity	Toxicological Significance**/Comments
1	A	DD-1	Methyl Alcohol (Skin)	MAL	58	14	200	250	--	Initial Tank Sampling	MMRL (A)
	A	DD-3	Methyl Alcohol (Skin)	MAL	12	249	200	250	--	Tank Top-Off	
	A	DD-5	Methyl Alcohol (Skin)	MAL	20	32	200	250	--	Final Tank Sampling	
	B	DD-2	Methyl Alcohol (Skin)	MAL	56	21	200	250	--	Initial Tank Sampling	
	B	DD-4	Methyl Alcohol (Skin)	MAL	21	42	200	250	--	Final Tank Sampling	
2	C	EX-16	Trichloroethane	TCE	122	4.5	350	450	--	Repetitive Gauging of Four Tanks by One Worker	MMRL (C)
			Trichloroethylene	TCL	122	0.7	50	150	--	"	
			Tetrachloroethylene	TTE	122	1.2	50	--	--	Worker	
			Styrene	STY	122	0.8	50	100	--	"	
	C	DW-1	Trichloroethane	TCE	116	8.6	350	450	--	"	
			Trichloroethylene	TCL	116	0.2	50	150	--	"	
			Tetrachloroethylene	TTE	116	25.6	50	--	--	"	
			Styrene	STY	116	N.D.	50	100	--	"	
	C	DW-6	Trichloroethane	TCE	126	9.0	350	450	--	"	
			Trichloroethylene	TCL	126	0.1	50	150	--	"	
			Tetrachloroethylene	TTE	126	7.2	50	--	--	"	
			Styrene	STY	126	N.D.	50	100	--	"	
	C	DW-8	Trichloroethane	TCE	46	4.4	350	450	--	"	
			Trichloroethylene	TCL	46	N.D.	50	150	--	"	
			Tetrachloroethylene	TTE	46	N.D.	50	--	--	"	
			Styrene	STY	46	N.D.	50	100	--	"	
	D	UCC-114	Trichloroethane	TCE	121	6.3	350	450	--	Repetitive Gauging of Four Tanks by Second Worker	NTS (D)
			Trichloroethylene	TCL	121	0.3	50	150	--	"	
			Tetrachloroethylene	TTE	121	1.8	50	--	--	"	
			Styrene	STY	121	2.2	50	100	--	"	
	D	DW-5	Trichloroethane	TCE	116	8.9	350	450	--	"	
			Trichloroethylene	TCL	116	0.3	50	150	--	"	
			Tetrachloroethylene	TTE	116	19.7	50	--	--	"	
			Styrene	STY	116	N.D.	50	100	--	"	
	D	DW-4	Trichloroethane	TCE	116	3.7	350	450	--	"	
			Trichloroethylene	TCL	116	N.D.	50	150	--	"	
			Tetrachloroethylene	TTE	116	1.7	50	--	--	"	
			Styrene	STY	116	N.D.	50	100	--	"	
	D	DW-9	Trichloroethane	TCE	48	N.D.	350	450	--	"	
			Trichloroethylene	TCL	48	N.D.	50	150	--	"	
			Tetrachloroethylene	TTE	48	N.D.	50	--	--	"	
			Styrene	STY	48	N.D.	50	100	--	"	

* Data from Table V.2 on pages 248, 249 and 250 of Reference 1.

** MMRL = Exposure meets criterion of medical monitoring response level.

NTS = Not of toxicological significance because exposure concentration is below medical monitoring response level.

TABLE IV-2. SINGLE SHIFT OR OPERATIONS ORIENTED EXPOSURES (Continued)

Seq-uence No.	Pers. Des.	Sample No.	Chemical	Chem. Abr.	Sampling Duration (min.)	Exposure Conc. (ppm)	TLV-TWA (ppm)	TLV-STEL (ppm)	TLV-C (ppm)	Work Activity	Toxicological Significance**/ Comments
3	E	SB-14	Benzene	BNZ	89	3.6	10	25	--	Tank Cleaning, Deckside, BNZ in Gasoline	MTS
	E	SB-20	Benzene	BNZ	387	1.6	10	25	--		
4	F	SB-1	Benzene	BNZ	194	5.2	10	25	--	Periodic Open Tank Gauging, BNZ in Gasoline	MMRL (F)
	F	SB-4	Benzene	BNZ	232	5.1	10	25	--		
	G	SB-2	Benzene	BNZ	165	2.4	10	25	--	Periodic Open Tank Gauging, BNZ in Gasoline	MMRL (G)
	G	SB-3	Benzene	BNZ	254	7.8	10	25	--		
	G	SB-5	Benzene	BNZ	201	6.3	10	25	--		
5	H	SB-12	Benzene	BNZ	81	0.9	10	25	--	Deck, Product Discharge, BNZ in Gasoline	MTS (H, I)
	I	SB-13	Benzene	BNZ	225	0.2	10	25	--		
6	J	SS-1	Methyl Ethyl Ketone	MEK	77	<1	200	300	--	Shore-Stop Tank Loading	MTS (J, K, L, M)
	J	SS-2	Methyl Ethyl Ketone	MEK	97	<0.5	200	300	--		
	K	SS-10	Methyl Ethyl Ketone	MEK	82	2.6	200	300	--	Shore-Stop Tank Loading	
	K	SS-11	Methul Ethyl Ketone	MEK	60	<0.6	200	300	--		
	L	SS-30	Methyl Ethyl Ketone	MEK	67	1.6	200	300	--	Final Stages Tank Loading Including Line Blowing	
	M	SS-40	Methyl Ethyl Ketone	MEK	52	4.0	200	300	--		
7	N	PS-7	Ethyl Alcohol	EAL	261.5	2.5	1000	--	--	Restricted Tank Gauging During TOL and MEK Loading	MTS (N, O, P)
			Toluene	TOL	261.5	0.7	100	150	--		
			Methyl Ethyl Ketone	MEK	261.5	N.D.	200	300	--		
	O	PS-8	Ethyl Alcohol	EAL	133.3	61	1000	--	--	Restricted Tank Gauging During TOL and MEK Loading	
			Toluene	TOL	133.3	0.3	100	150	--		
			Methyl Ethyl Ketone	MEK	133.3	N.D.	200	300	--		
	P	PS-9	Ethyl Alcohol	EAL	255.5	20	1000	--	--	Restricted Tank Gauging During TOL and MEK Loading	
			Toluene	TOL	255.5	0.4	100	150	--		
			Methyl Ethyl Ketone	MEK	255.5	0.1	200	300	--		

* Data from Table V.2 on pages 248, 249 and 250 of Reference 1.

** MMRL = Exposure meets criterion of medical monitoring response level.

NTS = Not of toxicological significance because exposure concentration is below medical monitoring response level.

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TABLE IV-2. SINGLE SHIFT OR OPERATIONS ORIENTED EXPOSURES (Continued)

Sequence No.	Pers. Pos.	Sample No.	Chemical	Chem. Abr.	Sampling Duration (min.)	Exposure Conc. (ppm)	TLV-TWA (ppm)	TLV-STEL (ppm)	TLV-C (ppm)	Work Activity	Toxicological Significance**/Comments
8	Q	UCC-115	Chloroform	CRF	94.5	47	10	50	--	Tank Cleaning, Stripping and Ventilation.	MMRL (Q)
	Q	UCC-112	Chloroform	CRF	33	21	10	50	--		
	Q	DW-14	Chloroform	CRF	5	N.D.	10	50	--	Tank Entry	
	R	DW-12	Chloroform	CRF	3	N.D.	10	50	--	Tank Entry	MMRL (R)
9	S	VF-6	Methyl Ethyl Ketone	MEK	172	0.92	200	300	--	Periodic Tank Gauging During Loading; Restricted Gauging (MEK, EAL) Closed Gauging (EPC).	NTS
			Epichlorohydrin (skin)	EPC	172	0.47	2	5	--		
			Ethyl Alcohol	EAL	172	0.16	1000	--	--		
	S	VF-6	o,m,p-Xylene	XLO,M,P	106	0.28	100	150	--	Restricted Tank Gauging During Loading.	
10	T	VF-14	Methyl Ethyl Ketone	MEK	202	0.09	200	300	--	Predischarge Ullage and Product Temperature Measurements	NTS (T, U)
			Epichlorohydrin (skin)	EPC	202	0.10	2	5	--		
			Ethyl Alcohol	EAL	202	0.41	1000	--	--		
			o,m,p-Xylene	XLO,M,P	202	0.25	100	150	--		
	U	VF-12	Methyl Ethyl Ketone	MEK	110	0.78	200	300	--	Restricted Tank Gauging During Discharge	
			Epichlorohydrin	EPC	110	0.38	2	5	--		
			Ethyl Alcohol	EAL	110	2.76	1000	--	--		
			o,m,p-Xylene (skin)	XLO,M,P	110	0.21	100	150	--		
11	T	VF-20	Methyl Ethyl Ketone	MEK	93	N.D.	200	300	--	Restricted Tank Gauging During Discharge	NTS
			Epichlorohydrin (skin)	EPC	93	0.12	2	5	--		
			Ethyl Alcohol	EAL	93	0.80	1000	--	--		
			o,m,p-Xylene	XLO,M,P	93	N.D.	100	150	--		
	T	VF-18	n-Butyl Alcohol (skin)	BAN	176	4.4	--	--	50	Restricted Tank Gauging During Discharge	
12	V	VF-15	Benzene	BNZ	141	0.14	10	25	--	Restricted Tank Gauging During Ballasting of Gasoline Tanks	NTS

* Data from Table V.2 on pages 248, 249 and 250 of Reference 1.

** MMRL = Exposure meets criterion of medical monitoring response level.

NTS = Not of toxicological significance because exposure concentration is below medical monitoring response level.

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trial illness has not been significant (41). Although there are some conflicting data, epidemiological studies of industrial workers indicate that relatively high concentrations of MAL can be inhaled without adverse effects. For example, Sterner (41) estimated that workers engaged in the manufacture of photographic film were exposed to daily average concentrations between 400 and 500 ppm without showing any evidence of MAL intoxication. In a study of the wood heel industry in Massachusetts, average MAL concentrations of 160 to 780 ppm were reported, without definite evidence of injury (7). Also, McAllister (42) reported concentrations between 400 and 1000 ppm in spirit duplicating processes without mention of symptoms or complaints. In contrast to these results, severe recurrent headaches were reported by Kingsley and Hirsch (43) in workers exposed to MAL in concentrations between 200 and 375 ppm; however, these exposures were over prolonged periods of time.

Animals such as mice, rats, dogs and rabbits vary in their tolerance to methyl alcohol (MAL) and, in general, can tolerate larger doses of MAL than humans (44). However, in rabbits exposed by inhalation to only approximately 50 ppm MAL for six months, ultrastructural changes in retinal cells and fibers were observed (45). Also, changes were noted in muscle activity and blood parameters in rats exposed continuously for 90 days to 4 ppm of this alcohol (46). In a significant animal study conducted by Sayers et al. (47), dogs were exposed eight hours per day to 450 to 500 ppm of MAL for 379 consecutive days. The animals did not show any unusual behavior, impairment of vision, loss of weight, ophthalmoscopic abnormalities, changes in blood or gross or microcopic abnormalities in tissues at necropsy. On the basis of this study, a limit of 200 ppm MAL was recommended by Cook for industrial exposures (7).

Thus, the industrial epidemiological data indicate that short exposures to the concentrations of methyl alcohol (MAL) measured in Sequence No. 1 would probably not produce any toxic effects or symptoms, other than mild irritation of the eyes and mucous membranes and possibly headaches. The limit values recommended by the ACGIH, OSHA and NIOSH are believed to incorporate a large margin of safety against serious toxic effects (7). However, MAL can be absorbed through the skin in sufficient quantities to cause severe toxic effects and even death (48). Therefore, workers entering tanks contain-

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ing residual MAL should wear appropriate protective clothing even when concentrations of the vapors are not excessive.

In Sequence No. 2, during repetitive gauging of four tanks, a crew member was exposed sequentially to mixtures of trichloroethane (TCE), trichloroethylene (TCL), tetrachloroethylene (TTE) and styrene (STY). In the samples collected during the approximately seven-hour monitoring period, the chemicals were either not detected or at very low concentrations, except in one sample. In this sample, the measured average concentration of TTE during the 116-minute exposure period was 25.6 ppm, which slightly exceeds 50 percent of the TLV-TWA (50 ppm) of this chemical. Although this concentration meets the criterion of a medical monitoring response level, human experimental data and industrial experience indicate that symptoms or effects would not result from this exposure. According to the Dow Chemical Company, which has had extensive experience with TTE, neither symptoms nor effects have been observed from 8-hour exposures to either 50 ppm or 100 ppm (40). The threshold concentration for eye irritation was reported as between 100 and 200 ppm, with minimal light-headedness occurring at 200 ppm, slight nasal irritation and incoordination at 400 ppm and dizziness and loss of inhibitions after exposure for 10 minutes to 600 ppm. These data are consistent with the results of several other investigators. As a result of extensive human studies of neurological, psychological and behavioral effects and of the volunteers' subjective responses, Hake and Stewart (49) concluded that 100 ppm TTE is probably without effect. These investigators also reported that alcohol consumption and drugs such as Diazepam® did not have an interactive effect with TTE on performance. In this particular sequence, concentrations of the other chemicals (TCE, TCL and STY) were considerably below levels at which biological interactions would be anticipated, even if interactions between these chemicals can occur.

In Sequence No. 4, two crew members were exposed to gasoline vapors during periodic open tank gauging while four tanks were loaded. The measured average concentrations of benzene (BNZ) in samples collected from the crewmen were generally above 5 ppm and, in one sample, the concentration was 7.8 ppm. Sampling durations were approximately 7 and 10 hours. Most of the measured concentrations exceed 50 percent of the TLV-TWA value (10 ppm) of BNZ

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and meet the criterion of a medical monitoring response level.

The primary symptoms that may result from acute inhalation of benzene (BNZ) are due to its effects on the central nervous system (10). At concentrations up to 25 ppm, inhalation of BNZ has been reported to be without effects but, at 50 to 150 ppm, headache, lassitude and weariness may occur and progress to drowsiness, dizziness, vertigo, loss of consciousness and death as concentrations increase to approximately 20,000 ppm. Other symptoms reported as a result of BNZ inhalation include giddiness and transient mild irritation of the respiratory and alimentrary tracts from an acute first-time moderate exposure and dyspnea, inebriation, euphoria, tinnitus and anesthesia from an acute high exposure. The rate of recovery from these effects depends on the concentration and duration of exposure, but symptoms may persist for several weeks following exposure.

Human chronic inhalation of benzene (BNZ) on a low-order repeated basis appears to be related to a variety of pathological conditions, particularly hematologic and myelotoxic effects (10). The levels of exposure at which these effects occur vary widely with individuals. Symptoms of chronic exposure include headache, dizziness, fatigue, anorexia, dyspnea, visual disturbances as well as vague symptoms, vertigo, pallor and loss of consciousness. Reported clinical effects from occupational exposures include hyperbilirubinemia, spleno- and adrenomegaly, various blood dyscrasias, hyperplastic bone marrow effects and increased chromosomal aberrations (10). There appear to be three stages of involvement from chronic BNZ exposures: low, intermittent exposures that result in very subtle hematopoietic changes; moderate to high exposures that affect enzyme synthesis, causing sensitizing effects and anemias; and high exposures producing irreversible blood dyscrasias.

Although the hematologic and myelotoxic effects of benzene (BNZ) have received the most attention, CNS involvement is also a primary toxic effect of chronic inhalation (10). At low chronic exposures, workers have exhibited signs of CNS lesions, abnormal caloric labyrinth irritability, impairment of hearing and neurological signs of polyneuritis. Also, it is possible that BNZ is a dermal sensitizer; continued skin contact causes de-

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fatting of the skin and may lead to erythema, dry scales and the formation of vesicular papules. Prolonged skin contact may produce lesions which resemble first- or second-degree burns. An additional potential target organ of BNZ is the heart. Benzene has been reported to cause tachycardia, decreased arterial pressure and peripheral resistance, and myocardial alterations which are reversible following termination of exposure (10). At extremely high levels, cardiac sensitization has been reported (50).

Benzene (BNZ) has also been designated a suspect carcinogen for man by the ACGIH because of a reported higher incidence of leukemia in certain industries in which workers were chronically exposed to this agent. Because of these reports, in 1976 NIOSH issued a revised recommendation to restrict occupational exposures to BNZ to "very low levels because it is not possible to establish a safe exposure level for a carcinogen" and, in 1977, OSHA issued an Emergency Temporary Standard (ETS) establishing a TWA limit of 1 ppm for BNZ vapor (7). Issuance of this ETS resulted in considerable debate by industry and enforcement of the standard was subsequently voided by the courts. Some of the data that were cited by the NIOSH and OSHA to support their actions were incomplete, unreliable and contradictory. Other data related to cited leukemia cases were associated with heavy BNZ exposures or were from epidemiologic studies on cancer in which no evidence of the degree, or even fact, of BNZ exposure was given. Furthermore, studies of workers who were exposed to measured low concentrations of BNZ have yielded negative or inconclusive results. Thus, considerable controversy still exists as to whether BNZ is a leukemogen (carcinogen), particularly at concentrations that do not exceed the TLV-TWA. The ACGIH Committee was of the opinion that the characterization of BNZ as a leukemogen by NIOSH was, in essence, valid, although it should be described as a suspect carcinogen based on the limited epidemiological evidence. However, the Committee did not agree with the NIOSH recommendation of 1 ppm as an occupational exposure standard in view of the fact that there is little evidence that exposure to BNZ at concentrations below 25 ppm causes blood dyscrasias of any kind.

It appears that a variety of factors may predispose some individuals' sensitivity to the toxic effects of benzene (BNZ) (10). These factors include age, nutrition, genetics, immunological tendencies and the consumption

of alcohol and drugs. The young appear to be more vulnerable to BNZ than adults and there is evidence that poor nutrition contributes to an increased susceptibility to BNZ. There is also evidence, mostly from animal studies, that some chemical or nutritional agents administered preceding, following, or in combination with BNZ can have synergistic or antagonistic effects. For example, barbiturates partially reverse benzene-initiated decreased weight gains and lymphopenia in the rat; they also increase the rate of BNZ metabolism up to tenfold. In some European industries, the development of cases of leukemia has been attributed to the inhalation of BNZ with other solvents such as cyclohexane. There is also evidence that the action of BNZ and lead in causing hematopoietic effects may be additive. Physical stress, such as vibration, and low and high temperatures have been reported to increase the toxicity of BNZ (10, 51). Conversely, ascorbic acid, B vitamins, steroids, and iron sorbitol have been found to counteract the toxic effects of BNZ, and the results of recent studies indicate that simultaneous administration of toluene reduces the toxicity of BNZ in rats (52, 53).

In summary, available epidemiologic data indicate that toxic effects are not likely as a result of exposures to benzene (BNZ) in Sequence No. 4. However, there is evidence that BNZ is a carcinogen and may cause leukemia in humans. Furthermore, there is considerable variation in individual susceptibility to BNZ toxicity and this toxicity may be enhanced by any of several factors. Therefore, an exposure to BNZ equal to or in excess of 50 percent of the TLV-TWA warrants medical monitoring of the worker as well as actions to limit the exposure of individuals to the vapors of this chemical.

In Sequence No. 8, a crewman was exposed to measured average concentrations of 47 and 21 ppm chloroform (CRF) vapors for approximately two hours during tank cleaning operations. These concentrations exceed the TLV-TWA value (10 ppm) for CRF and meet the criterion of a medical monitoring respone level. Although CRF was not detected in samples collected during tank entry by this crewman and another (probably because of the short sampling times), subsequent OVA measurements in the tank showed that CRF concentrations were in excess of the TLV-TWA and TLV-STEL values and meet the criterion of a medical monitoring response level.

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The chloroform (CRF) concentrations in the samples collected during this sequence are slightly greater than those in the samples of Sequence No. 17 of the single event exposures. The exposure duration of Sequence No. 8 also was longer than that of Sequence No. 17. Nevertheless, the Tier II assessment of CRF exposures in Sequence No. 17 of Section IV.3.1 is applicable to the exposures of this sequence. Literature reports, although limited, of acute and chronic clinical cases resulting from inhalation of CRF vapors indicate that symptoms or toxic effects would probably not result from the exposure of Sequence No. 8, unless exposure was more prolonged and occurred frequently. Nevertheless, the concentrations of CRF do exceed Threshold Limit Values and meet the criterion of a medical monitoring response level. These exposures are of particular significance because CRF is a suspected human carcinogen, and it is not possible to determine a safe exposure level for carcinogens. Therefore, efforts should be made to eliminate or at least to reduce exposure of workers to CRF and other suspect carcinogens.

IV.3.3 Sequential and Simultaneous Exposures During Terminal Loading Operations

The exposures in this category occurred during marine terminal operations in which 19 chemicals were loaded and one chemical was discharged from a tanker at eight terminal dockings. The majority of the data was collected during tank gauging. Since the vessel did not have restricted gauging systems, tanks were open-loaded and open-gauged.

Tier I Evaluations

The measured exposure data collected from four crew members during gauging operations (1) are summarized in Table IV-3. In the case of two of these crew members, the data were collected over consecutive and non-consecutive deck watches during which the individuals were exposed to mixtures of chemicals. The other two crewmembers were exposed to mixtures of chemical vapors during a single deckwatch. Each of the four exposure sequences was evaluated to determine whether the concentration of chemical and concentrations of mixtures of chemicals equal or exceed 50 percent of the TLV-TWA value for the chemical or mixture and thus meet the criterion of a medical monitoring response level.

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TABLE IV-3. SEQUENTIAL AND SIMULTANEOUS EXPOSURES DURING TERMINAL LOADING OPERATIONS*

	Sample No.	Chemical	Chem. Abr.	Sampling Duration (min.)	Exposure Conc. (ppm)	TLV-TWA (ppm)	TLV-STEL (ppm)	TLV-C (ppm)	Work Activity	Tox Signif.**/ Comments
A/B1	500	Trichloromethane	DCM	121	2.3	100	500	--		NTS
		Carbon Tetrachloride (Skin)	CBT	121	<0.3	5	20	--	Deck Hatch No. 1	
A/B1	501	Dichloromethane	DCM	133	2.1	100	500			NTS
		Carbon Tetrachloride (Skin)	CBT	133	<1.0	5	20			
A/B1	505	Dichloromethane	DCM	140	<0.2	100	500	--		NTS
		Carbon Tetrachloride (Skin)	CBT	140	<0.2	5	20	--	Deck Hatch No. 2	
		Trichloroethane	TCE	140	<0.1	350	450	--		
A/B1	507	Ethyl Acrylate (Skin)	EAC	69	<0.1	5	25	--		NTS
A/B1	508	Diethanolamine	DEA	66	<0.6	3	--	--		
A/B1	511	Ethyl Acrylate (Skin)	EAC	151	<0.1	5	25	--	Deck Hatch No. 5	
A/B1	512	Diethanolamine	DEA	93	<0.4	3	--	--		
A/B1	517	o-Dichlorobenzene	DBO	63	<0.3	--	--	50		
		p-Dichlorobenzene	DBP	63	<0.6	75	110	--		
A/B1	513	o-Dichlorobenzene	DBO	16	<0.3	--	--	50		
		p-Dichlorobenzene	DBP	16	<0.3	75	110	--		
A/B1	519	Ethyl Acrylate (Skin)	EAC	70	<0.4	5	25	--		MMRL
		Chloroform	CRF	70	7.9	10	50	50		
		o-Dichlorobenzene	DBO	70	<0.3	--	--	50	Deck Hatch No. 7	
		p-Dichlorobenzene	DBP	70	<0.3	75	110	--		
A/B1	521	Ethyl Acrylate (Skin)	EAC	60	<0.5	5	25	--		
		Chloroform	CRF	60	<1.7	10	50	50		
		o-Dichlorobenzene	DBO	60	<0.4	--	--	50		
		p-Dichlorobenzene	DBP	60	<0.4	75	110	--		

* Data from Table V.3 on pages 271 and 272 of Reference 1.

** MMRL = Exposure meets criterion of medical monitoring response level.

NTS = Not of toxicological significance because exposure concentration is below medical monitoring response level.

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TABLE IV-3. SEQUENTIAL AND SIMULTANEOUS EXPOSURES DURING
TERMINAL LOADING OPERATIONS* (Continued)

Sequence No.	Pers. Des.	Sample No.	Chemical	Chem. Abr.	Sampling Duration (min.)	Exposure Conc. (ppm)	TLV-TWA (ppm)	TLV-STEL (ppm)	TLV-C (ppm)	Work Activity	Tox. Signif.**/ Comments
2	A/B2	100	Carbon Tetrachloride (Skin)	CBT	126	10.4	5	20	--		MMRL
			Dichloromethane	DCM	126	<0.9	100	500	--		
			Trichloroethane	TCE	126	2.1	350	450	--	Deck Watch No. 1	
	A/B2	101	Carbon Tetrachloride (Skin)	CBT	117	9.2	5	20	--		
			Dichloromethane	DCM	117	<0.25	100	500	--		
			Trichloroethane	TCE	117	2.3	350	450	--		
	A/B2	102	Carbon Tetrachloride (Skin)	CBT	134	0.5	5	20	--		NTS
			Dichloromethane	DCM	134	<0.2	100	500	--		
			Trichloroethane	TCE	134	0.5	350	450	--	Deck Watch No. 2	
	A/B2	104	Diethanolamine	DEA	107	<0.3	3	--	--		
	A/B2	105	Ethyl Acrylate (Skin)	EAC	102	<0.07	5	25	--	Deck Watch No. 3	NTS
	A/B2	106	Ethyl Acrylate (Skin)	EAC	110	<0.07	5	25	--		
5	A/B3	528	Ethyl Acrylate (Skin)	EAC	73	<0.1	5	25	--		
			Toluene	TOL	73	1.6	100	150	--		
			n-Butyl Acrylate	BTC	73	<0.07	10	--	--		
		529	Methyl Methacrylate	MMA	59	<2.0	100	125	--		
		530	Ethyl Acrylate (Skin)	EAC	71	1.1	5	25	--	Deck Watch No. 11	NTS
		531	Methyl Methacrylate	MMA	71	<1.7	100	125	--		
		532	Ethyl Acrylate (Skin)	EAC	59	<0.1	5	25	--		
			Toluene	TOL	59	0.5	100	150	--		
			n-Butyl Acrylate	BTC	59	<0.09	10	--	--		
		533	Methyl Methacrylate	MMA	59	<2.0	100	125	--		

* Data from Table V.3 on pages 271 and 272 of Reference 1.

** MMRL = Exposure meets criterion of medical monitoring response level.

NTS = Not of toxicological significance because exposure concentration is below medical monitoring response level.

TABLE IV-3. SEQUENTIAL AND SIMULTANEOUS EXPOSURES DURING TERMINAL LOADING OPERATIONS* (Continued)

Sequence No.	Pers. Des.	Sample No.	Chemical	Chem. Abr.	Sampling Duration (min.)	Exposure Conc. (ppm)	TLV-TWA (ppm)	TLV-STEL (ppm)	TLV-C (ppm)	Work Activity	Tox. Signif.**/ Comments
4	A B4	114	Ethyl Acrylate (Skin)	EAC	68	2.4	5	25	--		
			Toluene	TOL	68	15.6	100	150	--		
			n-Butyl Acrylate	BTC	68	2.6	10	--	--		
		115	Methyl Methacrylate		54	<2.1	100	125	--		
		116	Ethyl Acrylate (Skin)	EAC	82	<0.1	5	25	--		
			Toluene	TOL	82	3.2	100	150	--	Deck Watch No. 11	NTS
			n-Butyl Acrylate	BTC	62	1.5	10	--	--		
		117	Methyl Methacrylate		82	<1.4	100	125	--		
		120	Ethyl Acrylate (Skin)	EAC	54	1.1	5	25	--		
			Toluene	TOL	54	5.7	100	150	--		
			n-Butyl Acrylate	BTC	54	3.3	10	--	--		
		121	Methyl Methacrylate		54	<2.1	100	125	--		

* Data from Table V.3 on pages 271 and 272 of Reference 1.

** MMRL = Exposure meets criterion of medical monitoring response level.

NTS = Not of toxicological significance because exposure concentration is below medical monitoring response level.

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In two of the exposure sequences (Sequence Nos. 3 and 4), the measured concentrations of chemicals in all of the samples were very low. These concentrations do not equal or exceed 50 percent of the TLV-TWA values for the individual chemicals or for the mixture of chemicals and do not meet the criterion of a medical monitoring response level. In Sequence No. 1, measured concentrations of chemicals to which the crewman was exposed during Deck Watch Nos. 1, 2 and 3 are below 50 percent of the TLV-TWA value of the chemical and the mixture of chemicals and are not considered toxicologically significant. However, during Deck Watch No. 7 of Sequence No. 1, the concentration of chloroform (CRF) in one Sample does exceed 50 percent of the TLV-TWA value and meets the criterion of a medical monitoring response level. Also, in Sequence No. 2, the concentrations of chemicals are below TLV-TWA values of the chemicals or mixtures during three deck watches (Nos. 2, 3 and 11). During Deck Watch No. 1 of this sequence, concentrations of carbon tetrachloride (CBT) in two samples exceed 50 percent of the TLV-TWA and thus meet the criteria of a medical monitoring response level. In-depth toxicological assessments of Sequence Nos. 1 and 2 are presented in the following Tier II evaluations.

Tier II Evaluations

During Deck Watch No. 7 of Sequence No. 1, a crewman was exposed for approximately three and one-half hours to vapors of both o-dichlorobenzene (DBO) and p-dichlorobenzene (DBP) and for approximately two hours to both ethyl acrylate (EAC) and chloroform (CRF). With the exception of CRF in one sample, the concentrations of the chemicals in all samples are very low and not of toxicological significance. In one sample (No. 519), the CRF concentration exceeds 50 percent of the TLV-TWA value and meets the criterion of a medical monitoring response level. Although toxic effects at this concentration are unlikely (see discussion of CRF toxicity in Section IV.3.1), CRF is a suspect carcinogen and workers exposed to CRF at these levels should be medically monitored. Also, efforts should be made to limit exposures to CRF and other suspect carcinogens in order to minimize the potential for carcinogenicity as a result of repetitive exposures or possibly additive effects of the chemicals. Although all four chemicals to which the crewman was exposed during this deck watch are hepatotoxic, the measured concentrations are very

and toxic effects on the liver from this exposure would not be anticipated.

In Sequence No. 2, the crewman was exposed during the first deck watch to measured average concentrations of carbon tetrachloride (CBT) of 10.4 and 9.2 ppm for 126 and 117 minutes, respectively. Other chemical vapors present in the samples are at very low concentrations and their contribution to the exposure is negligible. The exposure to CBT, however, exceeds the TLV-TWA value for this chemical and meets the criterion of a medical monitoring response level.

The primary target organs of carbon tetrachloride (CBT) are the central nervous system, the liver and the kidney (40). Exposure to high concentrations results in depression of the CNS and a loss of consciousness if the concentration is sufficiently high. At lower concentrations of CBT, symptoms of CNS depression include dizziness, vertigo, headache, depression, mental confusion and incoordination. Also, many individuals show gastrointestinal responses such as nausea, vomiting, abdominal pain and diarrhea. Functional and destructive injury of the liver and kidney may occur from a single acute exposure, but it is much more likely to occur from repeated exposures. In the case of long-term chronic exposure to low concentrations of CBT, kidney and liver injury dominate the clinical picture. The milder the exposure, the more the tendency for the injury to be predominantly in the liver. The concurrent intake of or exposure to substances which cause an increase in the activity of the microsomal drug metabolizing enzyme system (such as ethanol, barbiturates and chlorinated biphenyls) increase the toxicity of CBT and may greatly increase the probability of liver injury (7). Several cases of liver cancer in animals and humans exposed to CBT have been reported and, therefore, CBT has been classified as a suspect human carcinogen by the ACGIH. In all of the human cases, the patients had been acutely overexposed to CBT, leading to nausea, stomach pains and other signs of severe liver damage (7).

Although there are many reports of acute inhalation poisonings by CBT, these reports generally lack sufficient precise information about exposure concentration to estimate a safe exposure dose (40). In one industrial exposure, Heimann and Ford reported that six workers exposed to 33 to 124 ppm

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of CBT became fatigued within two hours (7). In another industrial exposure, headaches and giddiness occurred in workers exposed to 45-97 ppm CBT. Stewart and others (7) reported that a 180-minute experimental exposure to 10-11 ppm did not affect liver function in humans. However, in animals exposed to 10 ppm CBT for weeks or months, there was detectable accumulation of fat in the liver. On the basis of these animal experiments and the reported potentiation of CBT toxicity by alcohol and other substances, a time-weighted average TLV of 5 ppm was recommended by the ACGIH to protect against damage to the liver and the development of liver cancer (7). A short-term exposure limit (TLV-STEL) of 20 ppm was recommended by the ACGIH to avoid the occurrence of fatigue and other CNS symptoms. The ACGIH has identified CBT with a "Skin" notation to indicate that CBT can be absorbed through the skin in sufficient quantities to cause toxic effects and invalidate Threshold Limit Values. Therefore, precautions should be taken to avoid dermal contact with CBT liquid or vapor by the wearing of appropriate protective clothing.

From the available literature reports, it is not anticipated that single exposures to CBT typical of Sequence No. 2 would cause symptoms or toxic effects. However, it is possible that repeated exposures of this magnitude could produce injury to the liver and such exposures should be of concern. In addition, marine operations provide the opportunity for exposures of extended duration as well as for simultaneous exposures to other chemicals which have hepatotoxic, nephrotoxic and carcinogenic effects and could interact with CBT and enhance its toxicity. Therefore, crewmen exposed to CBT at the levels in Sequence No. 2 should be medically monitored. In addition, efforts should be made to limit exposures to CBT and to other chemicals with carcinogenic potential.

IV.3.4 Exposures to Carcinogens

In each of the categories of measured exposure sequences, crewmen were exposed to at least one chemical with suspected carcinogenic potential at a concentration that exceeds the TLV-TWA and meets the criterion of a medical monitoring response level. In the single event exposures, crewmen were exposed during tank entry to concentrations of chloroform (CRF) that exceed the TLV-TWA value. During open tank gauging of gasoline tanks in single shift/op-

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erations oriented exposures, crewmen were exposed to benzene (BNZ) at levels greater than 50 percent of the TLV-TWA. During tank cleaning and tank entry, concentrations of CRF exceed the TLV-TWA of this chemical. In the sequential/simultaneous exposure category, terminal loading operations resulted in exposure to CRF at a concentration greater than 50 percent of the TLV-TWA and to CBT at a concentration that exceeds the TLV-TWA. Since BNZ, CRF and CBT represent only three of the 11 Subchapter D and Subchapter O substances designated carcinogens by the ACGIH, it is apparent that there is considerable potential for exposure to carcinogenic substances during marine operations.

The development of cancer is a long-term process, with symptoms appearing many years after exposure to the carcinogen. Thus, the disease is insidious because there is no warning or feedback to the exposed individual during the exposure period. Because of the long time interval between exposure and appearance of symptoms, our knowledge of the threshold effect dose of these chemicals is usually very limited. Most of our knowledge has been obtained from retrospective epidemiological studies of industrial workers who were exposed eight hours daily for several years. In many cases, concentrations of the chemical were not measured and only estimates are available. Usually, these exposures involved a single carcinogenic chemical. In contrast, in the marine environment, crewmen may be exposed repeatedly or for prolonged periods to a single carcinogen or to mixtures of carcinogens with possible interactive effects. During certain activities, the potential exists for exposure to concentrations that exceed allowable limit values. Other factors in the marine environment such as temperature extremes, stress and dietary deficiencies also may enhance the carcinogenic potential of these exposures.

Because exposures and conditions in the marine environment are unique and differ considerably from those in industry, even less is known about the potential for development of cancer from exposures to chemicals during marine operations. Since a "safe" level of exposure to any of the carcinogenic chemicals should not be assumed, the following conservative approach may be taken to reduce the probability of development of cancer from these exposures:

° Marine workers should be made aware of the identity of carcinogenic chemicals and of the fact that the effect of these chemicals may not occur until many years after exposure. Extreme precautions should be taken by marine workers to avoid exposure to chemicals designated carcinogens as well as to other chemicals.

° An industrial hygiene program to control exposures to all chemicals should be implemented. The aim of this program should be to reduce exposure levels to the lowest possible level and certainly to below Threshold Limit Values.

° All exposures of personnel to carcinogenic substances should be recorded because it is unlikely that any program will completely eliminate all exposures to carcinogenic substances. This information should be used (1) to establish the data base for an epidemiological study for public health use, (2) to enable possible restriction of marine workers from ships transporting carcinogenic chemicals when these workers have reached a certain exposure level, as established by occupational medical personnel, and (3) to correlate with medical monitoring findings.

° All personnel exposed to carcinogenic chemicals should be medically monitored to determine if excessive exposure has occurred and to detect early signs of disease.

IV.3.5 Hypothetical Combinations of Measured Exposures

The occupational exposure data presented in the preceding sections were obtained from the actual monitoring of maritime personnel exposed to chemical vapors. Concentrations of these vapors were provided by the analyses of more than 200 exposure samples collected from crew members engaged in a variety of work functions, including tank entry, tank gauging and various on-deck activities. The toxicological evaluation of each exposure sequence was made on the basis of measured data.

The exposure sequences that were monitored and the resultant occupational exposure data serve a useful purpose in identifying potentially hazardous work activities involving specific chemicals. However, it should be emphasized that these sequences represent a small fraction of the many possible types of exposures that occur during maritime operations. For example, in the marine operations monitored during this study, tank entries primarily resulted in single event exposure sequences. It is also possible that the

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same crewman who is exposed during tank entry will subsequently perform gauging activities and be exposed to the same chemical or to other chemicals. In order to provide a more complete representation of maritime exposures, various hypothetical combinations were formed from the measured exposure data and these combinations were evaluated for toxicological significance. The results of these evaluations are discussed in the following sections.

Tier I Evaluations

Three hypothetical exposure sequences in which measured exposure data were combined are summarized in Table IV-4. These data are identified in the table by their original sequence and table numbers. The same criterion was used for the Tier I evaluation of these hypothetical combinations of measured exposures as for the individual measured exposures. If the concentration of a chemical or a mixture of chemicals is less than 50 percent of the TLV-TWA value of the chemical or mixture, the exposure does not meet the criterion of a medical monitoring response level and is not considered to be toxicologically significant. If the concentration equals or exceeds 50 percent of the TLV-TWA value of the chemical or mixture, the exposure does meet the criterion of a medical monitoring response level and is considered toxicologically significant. In the first hypothetical combination sequence (Sequence No. 1), concentrations of chemicals are below 50 percent of TLV-TWA values and do not meet the criterion of a medical monitoring response level. In the other sequences (Sequence Nos. 2 and 3), concentrations of some chemicals do equal or exceed 50 percent of TLV-TWA values and meet the response level criterion. In-depth toxicological evaluations of these exposures are presented in the following Tier II evaluations.

Tier II Evaluations

In Sequence No. 2, a sequential 40-minute in-tank exposure to chloroform (CRF) at average concentrations ranging from 14.0 to 31.7 ppm was preceded by an in-tank exposure to ethyl alcohol (EAL) for 30 minutes. The concentration of EAL is less than 50 percent of the TLV-TWA (1000 ppm) but the concentrations of CRF exceed the TLV-TWA (10 ppm) and meet the criterion of a medical monitoring response level. The combined exposure to these two chemi-

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TABLE IV-4. HYPOTHETICAL COMBINATIONS OF MEASURED EXPOSURES*

Hypoth. Seq. No.	Measured Sequence No. (Table)	Chemical	Chemical Abbreviation	Exposure Duration, (min)	Exposure Conc. (ppm)	TLV-TWA (ppm)	TLV-STEL (ppm)	TLV-STEL (ppm)	Work Activity	Tox. Signif.*/ Comments
1	6J (IV-2)	Methyl Ethyl Ketone	MEK	77	<1	200	300	--	Tank Loading	NTS
		Methyl Ethyl Ketone	MEK	97	<0.5	200	300	--		
	6K (IV-2)	Methyl Ethyl Ketone	MEK	82	2.6	200	300	--	Tank Loading	
		Methyl Ethyl Ketone	MEK	60	<0.6	200	300	--		
	6L (IV-2)	Methyl Ethyl Ketone	MEK	67	1.6	200	300	--	Tank Loading	
	6M (IV-2)	Methyl Ethyl Ketone	MEK	52	4.0	200	300	--	Tank Loading	
	7N (IV-2)	Ethyl Alcohol	EAL	261.5	2.5	1000	--	--	Restricted Tank Gauging	
		Toluene	TOL	261.5	0.7	100	--	--		
		Methyl Ethyl Ketone	MEK	261.5	N.D.	200	300	--		
	9S (IV-2)	Methyl Ethyl Ketone	MEK	172	0.92	200	300	--	Tank Gauging	
		Epichlorohydrin (Skin)	EPC	172	0.47	2	5			
		Ethyl Alcohol	EAL	172	0.16	1000	--			
		o,m,p-Xylene	XLO,M,P	106	0.28	100	150			
2	15V (IV-1)	Ethyl Alcohol	EAL	30	>239**	1000	--	--	Tank Entry	MMRL
	17Y (IV-1)	Chlorform	CRF	15	31.7	10	50	--	Tank Entry	
		Chloroform	CRF	15	22.4	10	50	--		
		Chloroform	CRF	10	14.0	10	50	--		
3	12S (IV-1)	Methyl Ethyl Ketone	MEK	13	1.2	200	300	--	Ullage Port Sampling	MMRL
		o,m,p-Xylene	XLO,M,P	13	0.1	100	150	--		
	7M (IV-1)	n-Hexane	HXA	34.93	944	50	--	--	Tank Top-Off (O.G.)	

* MMRL = Exposure meets criterion of medical monitoring response level.

  NTS = Not of toxicological significance because exposure concentration is below medical monitoring response level.

** Possible vapor migration.

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cals is even more toxicologically significant because of potential biological interactions between EAL and CRF. Ethyl alcohol has been reported to potentiate the toxic effects of a number of halogenated hydrocarbons, including CRF, in animals. For example, studies by Kutob and Plaa (54) demonstrated increased toxicity and abnormal liver function in mice challenged with CRF after pretreatment with EAL. The investigators postulated that higher levels of liver lipids produced by EAL resulted in greater CRF retention. In addition, enhancement of the hepatotoxicity and/or nephrotoxicity of chlorinated hydrocarbons by several other chemicals (although these chemicals are not in this hypothetical sequence) and certain host factors have been demonstrated in animal studies. These chemicals include isopropyl alcohol, acetone, n-hexane and metyl n-butyl ketone (55, 56). Food deprivation and low carbohydrate intake also have been reported to enhance the hepatotoxicity of CRF in animals (57, 58). Although the relevance of these findings in animals has not been established in humans, the results do, nevertheless, suggest the possibility of similar interactions in humans.

Sequence No. 3 also represents a hypothetical combination of measured exposures in which the possibility for biological interactions exists and must be considered in evaluating the potential hazard to exposed crewmen. In this sequence, an exposure to a high average concentration (944 ppm) of n-hexane (HXA) during open gauging was preceeded by a short exposure to low concentrations of methyl ethyl ketone (MEK) and o,m,p-xylene (XLO,M,P) during ullage port sampling. The concentrations of MEK and XLO,M,P are below 50 percent of the TLV-TWA values for these chemicals and do not meet the criterion of a medical monitoring response level. However, the concentration of HXA exceeds the TLV-TWA (50 ppm) of this chemical and meets the criterion of this response level. The combined exposure is even more potentially hazardous because of possible biological interaction of MEK with HXA as well as with other chemicals. For example, Altenkirch and others (59) reported that MEK is capable of synergizing the neurotoxicity of HXA, resulting in the earlier development of more severe peripheral neuropathies. In this hypothetical exposure, the concentration of MEK may be too low to alter the toxicity of HXA; however, it is possible that repeated exposures or higher concentrations of MEK would have an effect.

IV.3.6 <u>Tank Cleaning and Entry with Dermal Contact with Chemicals</u>

Up to this point, all of the toxicological assessments have re-
flected actual measured exposure data and the corresponding documentation of
operations and work scenarios. Furthermore, these assessments have involved
only the inhalation route of chemical entry into the body.

Dermal exposures are also very important. When they do occur, the
exposure level is not easily quantified. For completeness, this section
addresses the toxicological implications of a dermal exposure that involves
selected chemicals during tank cleaning and entry. The scenario description,
which is presented below, is based on actual observation. The chemicals that
were selected have the ability to enter the body via the cutaneous route.

The ship had discharged all of its cargo, and after putting out to
sea, the product tanks were cleaned in preparation for biennial docking for
USCG inspection and repairs. Depending upon the chemicals involved, tanks
were either washed and then ventilated or only ventilated to achieve a gas
free condition. As the ship was to undergo internal inspection, it was neces-
sary to gas free the tanks below accepted exposure limits so that they could
be certified for entry by a Marine Chemist. This scenario applies to a tank
that was washed and then ventilated. Both of the chemicals that will be
considered in the interpretation of this scenario (phenol and aniline) are
very soluble in water.

Tank washing involved three crew members who lowered the washing
hose and nozzle 15 feet into the tank through a Butterworth opening. The hose
was secured with rope, the deck plate was propped against the hose and the
wash water was turned on. Periodically during the washing, liquid spray was
ejected onto the deck. The odor of chemical was present. At the conclusion
of the washing, all three crew members took part in removing the hose from the
tank. Two of the workers wore rubber boots while the third worker wore street
shoes. Hand protection included rubber and cotton cloth gloves or gloves were
not worn. This portion of the scenario suggests potential dermal exposures as
indicated below.

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      °   Two of the three crew members encountered a potential
dermal exposure of the hands to water-diluted chemical
when the washing hose was manually removed from the
tank. The wash water jets from the nozzle impinge on
the tank walls and the underside of the deck. The
resulting spray consists of residual chemical in solu-
tion. Some of the spray droplets are deposited on the
hose. Direct contact was assured for the individual
with no gloves. Any residual chemical on the hose
could penetrate the absorbent, cotton gloves.

      °   As the deck was damp from the washing spray, the in-
dividual with street shoes encountered a potential
dermal exposure of the feet. Chemical-water solutions
absorbed into the leather sole material would be re-
tained and could potentially migrate to the insole.

At the conclusion of the washing operation, the tank blower was turned on, and
the tank was ventilated continuously for the next 24 hours.

The second part of this scenario began after the 24-hour venti-
lation of the tank. The blower was turned off, and the Chief Mate entered the
tank to test the atmosphere using colorimetric detector tubes. The entry was
made without respiratory protection. The testing revealed that the vapor
concentration was considerably above the TLV-STEL. The tank had not gas
freed, during the 24-hour ventilation, because of vapor regeneration from
chemical/water residues and cargo-containing debris on the tank bottom.
Therefore, the tank would have to be entered, manually cleaned to remove the
debris and then ventilated again to produce an acceptable atmosphere for the
shipyard.

Four crew members entered the tank for a period of 18 minutes.
Their cleanup equipment included 2.5-gallon buckets, broom, dust pan, mops and
rags. As each bucket was filled with liquid or debris, it was hoisted to the
deck, and the contents were dumped overboard.

Two of the crew members concentrated on sweeping up damp rust
scale. Scale develops if the tank internals are not coated or if the coating
has deteriorated. Both of these individuals were dressed comparably-- short
sleeve shirts, cotton gloves, work pants and organic vapor cartridge respir-
ators. One of the crew members used the broom, and the other crew member hand

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swept the debris into the dust pan. The hand sweeping constitutes a potential dermal exposure of the hands. Unprotected skin surfaces were also exposed to the cargo vapor.

The other two crew members were responsible for cleaning out residual liquids in the pump sump. One of the individuals was dressed in shorts, open short-sleeved shirt, rubber gloves and leather-soled work boots. He also wore an organic vapor cartridge respirator, but the bottom retaining strap was not in place which nullified any protection. The other crew member wore coveralls, leather soled work boots, rubber gloves and a cartridge respirator. The procedure involved mopping up the residual liquid and wringing out the mop or rag into the bucket. During wringing, small liquid droplets splashed onto the exposed arms and legs of one crew member. The contacting liquids were washed from the skin approximately 2.5 hours later in a shower following the close of the work shift. The concentration of the chemical in the wash was unknown. Vapor contact with exposed skin also occurred.

In all, 14 buckets of debris and residual liquid were removed from the tank bottom. Each bucket was dumped overboard by a crew member who wore only leather gloves. The final bucket, which contained mostly liquid, was dumped on deck where it could come in contact with shoe materials.

In the above scenario, rubber boots and gloves were worn by some workers. The term "rubber" has been used generically because the exact type of protective material could not be determined.

Tier I Evaluations

In this scenario involving tank cleaning and entry, the assumption is made that the tank contained either residual phenol (PHN) or residual aniline (ANL). During the tank washing process, aqueous washing spray of the chemical is ejected onto the deck, providing the opportunity for inhalation of chemical vapor as well as for dermal absorption of the chemical (appropriate respirator equipment and protective clothing/footwear are not worn by all crew members). In addition, when the washing hose is removed from the tank, there
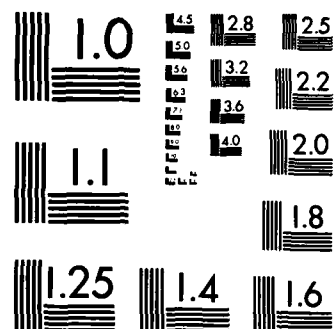
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is the possibility of dermal absorption of chemical when workers' hands are in contact with aqueous chemical solution deposited on the hose. There is also the opportunity during tank entry for both the inhalation of chemical vapors and dermal absorption of the chemical from aqueous solution splashed on the skin, unless proper respiratory and skin protection are provided. Finally, in the removal of buckets of debris and residual solution from the tank and in the dumping of these buckets overboard or on deck, dermal absorption is possible, unless the workers have adequate skin protection.

The vapor concentrations of phenol (PHN) and aniline (ANL) to which crew members are exposed on deck during tank washing is not known. Therefore, it is not possible to determine whether these concentrations equal or exceed 50 percent of the TLV-TWA values for these chemicals and meet the criterion of a medical monitoring response level. However, during this washing process, the potential for dermal absorption of toxic quantities of both chemicals appears much greater than for the inhalation route. The ACGIH has identified both PHN and ANL with a "Skin" notation to indicate that, unless preventative measures are taken, sufficient quantities of these chemicals may be dermally absorbed to cause toxic effects and invalidate Threshold Limit Values. Adequate protective clothing and footwear were not worn by all crew members in this scenario; therefore, the exposures of crew members to PHN or ANL during the washing process are assumed to exceed 50 percent of the TLV-TWA values and meet the criterion of a medical monitoring response level.

During tank entry by the Chief Mate and other crew members, the vapor concentration of phenol (PHN) or aniline (ANL) in the tank is assumed to exceed the TLV-TWA and TLV-STEL values for each chemical and thus meet the criterion of a medical monitoring response level. The hazardous nature of these exposures would be further increased by the probable dermal absorption of significant quantities of chemical during the cleaning of the tank and the dumping activities.

Tier II Evaluations

Because of its low volatility, phenol (PHN) does not frequently constitute a serious acute respiratory hazard in the industrial environment.

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In cases in which intermittent industrial exposures (five to ten minutes per hour) resulted in marked irritation of the nose, throat and eyes, average atmospheric concentrations were approximately 50 ppm (60). At average concentrations of 4 ppm, irritation was not experienced by industrial workers. Chronic inhalation of PHN may produce systemic toxic effects, although reports of cases of chronic poisoning have become very infrequent. Severe chronic toxicity is characterized by digestive disturbances (vomiting, difficulty of swallowing, diarrhea and anorexia) and nervous disorders (headache, fainting, vertigo and mental disturbances) (61). Fatalities may result when damage to the liver and kidneys is severe. A TLV-TWA value of 5 ppm was recommended by the ACGIH and NIOSH to avoid the systemic as well as the irritant effects of this chemical. This limit value, according to Thomas and Back (62), incorporates a sufficiently large safety factor to prevent systemic poisoning from the inhalation of PHN vapors.

Although phenol (PHN) is not ordinarily considered a serious respiratory hazard, the local and systemic effects that may result from skin contact with this chemical are of much concern. Cases of PHN poisoning from dermal absorption also have occurred among industrial workers as a result of accidental contact with the chemical (63). In a recent report, an accidental death resulted from the application of a scabicide to the body with a brush that had been placed in 80-percent PHN and had not been thoroughly washed before use (64). In a 1976 NIOSH criteria document (65), the potential hazard of dermal contact with PHN received considerable emphasis. This hazard is also recognized by the ACGIH in its identification of PHN with a "Skin" notation to call attention to the potential contribution of cutaneous absorption to the overall exposure to the chemical. Thus, even when the concentration of PHN vapor is below the TLV-TWA of 5 ppm, sufficient quantities may be absorbed through the skin to invalidate this limit value. The absorption of PHN through the skin has been studied in human volunteers by several investigators (63). Data from these experimental studies confirm the fact that PHN easily penetrates through human skin from aqueous solutions and that increasing the concentration or time of exposure leads to an increase in the amount of PHN absorbed. In addition, increasing the skin temperature from 20° to 35°C results in a significant increase in skin absorption.

In view of the considerable potential for dermal absorption of phenol (PHN) in this hypothetical scenario, the exposures during cleaning and entry of a tank containing residual PHN could result in serious toxic effects and even deaths of marine workers. Therefore, for such work activities, worker exposures should be controlled by compliance with recommendations contained in the NIOSH Recommended Standard for Occupational Exposure to Phenol (66). These recommendations specify procedures or equipment for medical monitoring, labeling and posting, personal protective equipment and protective clothing, informing employees of hazards from PHN, work practices, sanitation and monitoring and record keeping.

Aniline (ANL) is widely used in the chemical industry and occupational poisonings were at one time relatively common. Acute intoxication has been attributed to the formation of methemoglobin, although there are suggestions of some lesser effects due to ANL (67). Hemolysis of red blood cells has been suggested as a possible effect but there seems to be little supporting evidence, and, in human studies, it has not been found to be significant. Other effects reported in ANL poisonings include liver damage, bone marrow changes, respiratory tract inflammation and involvement of the gastrointestinal tract; however, there are insufficient data to confirm these findings. In a recent study of ANL in human volunteers, extensive hematologic and clinical chemical analyses detected no abnormalities other than increased methemoglobin content of the blood; however dosaging was limited to 65 mg of ANL per individual (68).

The outstanding clinical effect of aniline (ANL) intoxication is cyanosis due to the formation of methemoglobin (67). The onset of cyanosis involves the lips and ears and sometimes is referred to as "blue lips." Ordinarily, symptoms are few or even absent in the beginning, and even at a level of 40 percent methemoglobin there may be few symptoms. As the concentration increases, such symptoms as light headedness, ataxia and weakness occur. Further increases in concentration may cause tachycardia, dyspnea and obvious cyanosis. These effects are due to the oxidation of hemoglobin to methemoglobin, thereby making it incapable of its usual function of transporting oxygen to the tissues and organs of the body. When the oxygen transport capability is reduced sufficiently, toxic effects, including possible death,

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may result from chemical asphyxiation.

In view of the potential for dermal absorption of aniline (ANL) in this scenario, exposures during washing, entry and cleaning of a tank containing residual ANL may be extremely hazardous. In addition, vapor concentrations during tank entry exceed Threshold Limit Values. Aniline is fat-soluble and penetrates the intact skin rapidly; its vapors also are quickly absorbed upon inhalation or contact with the skin. Because this scenario could lead to exposures with serious toxic effects, including death, extreme precautions should be taken in all activities involving ANL tanks. Exposures should be controlled by compliance with recommendations contained in the NIOSH Recommended Standard for Occupational Exposure to Aniline (69) to ensure the protection of the safety and health of marine workers.

IV.4 Summary

It is apparent from the toxicological assessments of the measured exposure sequences that the marine environment is a potentially hazardous environment. In these sequences, crewmen were exposed to chemicals, some of which are regarded as highly toxic and cause serious damage to several organs and systems of the body. Examples of these chemicals are n-hexane, epichlorohydrin, ethylene dichloride, benzene, carbon tetrachloride and chloroform. Human epidemiologic and experimental animal data indicate that the latter three chemicals may be carcinogenic to man. In many of the measured exposure sequences, concentrations of all chemicals are very low do not meet the criterion of a medical monitoring response level. In other sequences, however, the concentrations do meet the criterion of a medical monitoring response level and are considered of toxicological significance. In some sequences, particularly those involving tank entry and open tank gauging, the measured concentrations exceed ACGIH and OSHA allowable limit values and are considered potentially hazardous. The potential hazards of such exposures may be increased by certain unique conditions of marine operations such as extended work schedules, sequential or simultaneous exposures to a number of chemicals having interactive effects, and stress. It should be possible to reduce toxicological hazards in the marine environment by educating workers in the need for precautionary measures, implementing an industrial hygiene program,

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recording and possibly limiting personnel exposures to carcinogenic chemicals and medically monitoring personnel receiving excessive exposures and exposures to carcinogens.

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V. TOXICOLOGICAL ASSESSMENTS OF HYPOTHETICAL EXPOSURE DATA

V.1 Introduction

In the previous section of this document, toxicologic assessments were made of occupational exposure data measured during routine marine work activities. In addition, assessments were made of a number of hypothetical exposure sequences that could result from combinations of work activities in which measured data were obtained. Although more than 200 exposure samples were collected during these work activities and analyzed, these measured data represent only a small fraction of the chemicals involved in marine operations. Therefore, the measured exposure data were supplemented with hypothetical but realistic exposure predictions for which certain operating conditions were assumed. The exposure data for these hypothetical sequences were predicted from the physical properties of the applicable marine chemicals and by the use of analytical computer modeling of tank ventilation and plume dispersion. The purpose of this section is to toxicologically assess these hypothetical exposure sequences.

V.2 Assessment Criteria

The same conservative two-tiered approach that was used for the measured occupational exposure data was followed in assessing the hypothetical exposure sequences. In the Tier I evaluations, the predicted data were screened in order to identify those exposures in which the concentration of chemical does not equal or exceed 50 percent of the ACGIH TLV-TWA value for the chemical. Those exposures do not meet the criterion of a medical monitoring response level and, therefore, did not require further evaluation. Those exposures in which the concentration of chemical equals or exceeds 50 percent of the TLV-TWA value meet the criterion of a medical monitoring response level and were further assessed toxicologically in Tier II evaluations.

V.3   Toxicological Assessments

V.3.1   Open Gauging

There are three systems or methods of gauging product ullage - open, restricted and closed. Of these three methods, open gauging, especially at tank top off, presents the greatest potential for occupational exposure to high concentrations of product vapors. The open gauging scenarios that were monitored in this project involved only a fraction of the chemicals that may be open gauged in marine operations. Therefore, the toxicological assessment of open gaguing exposures was extended to include other chemicals. The following discussion describes the criteria for chemical selection, prediction of exposure concentration and the tank top-off work scenario.

The Chemical Data Guide for Bulk Shipment by Water (USCG Publication CIM 16616.6, 1982) identifies the regulatory classification of 305 chemicals. This publication was used as the primary source document for chemical selection. The USCG also regulates approximately 400 additional products that do not yet appear in the guide. Each chemical in the guide was screened and eliminated from further consideration if:

    ° it is not allowed to be carried in bulk on tankers in U.S. waters:

    ° the minimum gauging requirements in Table 1 of 46CFR Part 153 (Safety Rules for Self-Propelled Vessels Carrying Hazardous Liquids, Oct. 1982 Edition) specify restricted or closed gauging systems;

    ° it was included in Table 4 of 46 CFR Part 154 (Safety Standards for Self-Propelled Vessels Carrying Bulk Liquified Gases, Oct. 1982 Edition); all products in this part require closed or restricted gauging systems;

    ° the product does not have a Threshold Limit Value as specified in the 1983-1984 Edition of the ACGIH TLV book; or

    ° the substance is an airborne particulate.

The exclusions based on minimum gauging requirements conform to USCG regulations. However, during actual operations, cargo ullage may be open

gauged contrary to regulatory requirements. These latter situations are not reflected in this assessment.

An exposure concentration was then estimated for each chemical that survived the above five exclusion criteria. The following estimation criterion was used:

$$\frac{C_e{}^*}{C_s} = \frac{C_{e,o}}{C_{s,o}}$$

where $C_e{}^*$ = estimated concentration for a given chemical;

C_s = saturation concentration for that chemical at 20°C;

$C_{e,o}$ = measured exposure concentration at tank top-off for reference chemicals;

$C_{s,o}$ = saturation concentration for reference chemicals at 20°C.

The above equation is a statement that the exposure concentration during tank top-off is proportional to the saturated vapor concentration of the chemical that is being loaded. This criterion is realistic because all open gauging ports are nearly the same height above the weather deck (breathing zone/ullage port separation distance is roughly constant) and vapor discharge concentrations at the end of loading approach or equal a saturation condition. Based on exposure monitoring during tank top-off for methanol, toluene and hexane (reference chemicals), the average value for $C_{e,o}/C_{s,o}$ is 6.9×10^{-3}. That is, $C_e{}^* = 6.9 \times 10^{-3} C_s$.

The constant, 6.9×10^{-3} was calculated using the measured exposure and vapor pressure data in Table V-1. Thus, top-off gauging exposures are lower than the chemical specific saturated vapor concentration by roughly a factor of 145.

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TABLE V-1. BASIS FOR $C_{e,o}/C_{s,o}$

	Methanol	Hexane	Toluene
Sample No.	01-P3	PE-5	PE-1
$C_{e,o}$ (ppm)	850	944	199
P_v (mm Hg, 20°C)	100	97	22
$C_{s,o}$ (ppm)	1.32×10^5	1.28×10^5	2.9×10^4
$C_{e,o}/C_{s,o}$	6.4×10^{-3}	7.4×10^{-3}	6.9×10^{-3}

$$\frac{C_{e,o}}{C_{s,o}} \text{ ave} = 6.9 \times 10^{-3}$$

At this point, two industrial hygiene criteria were imposed.

° Chemicals having an estimated exposure level in excess of the IDLH (immediately dangerous to life or health) concentration were eliminated from further consideration. Only one product, camphor oil, responded to this criterion under the assumption that the IDLH value for camphor could be applied to camphor oil. The source document for IDLH levels was the NIOSH/OSHA Pocket Guide to Chemical Hazards (DHEW Pub. No. 78-210, August 1980 Edition).

° Chemicals whose predicted exposure level was less than the medical monitoring response level (TLV-TWA/2) were eliminated from further consideration.

The chemicals that survived this screening process are shown in Table V-2.

Next, a tank top-off work scenario was specified. The scenario, which involves top-off of six cargo tanks, is based on observation and documentation of actual shipboard operations. The scenario ground rules are as follows:

° All six top-off operations are performed by a single Mate;

° Tanks are fully loaded (no short loading);

° A zero exposure level exists during the 8-hour rest periods before and after the 4-hour work shift of interest;

° Exposure levels are negligible except during tank top-off.

TABLE V-2. CANDIDATE CHEMICALS FOR TANK TOP-OFF EXPOSURE INTERPRETATION

Chemical	TLV-TWA (ppm)	C_e* (ppm)
Acetone	750	1634
IsoButyl Acetate	150	182
n-Butyl Acetate	150	79
Sec Butyl Acetate	200	185
Iso Butyl Alcohol	50	80
n-Butyl Alcohol	50	80
Sec Butyl Alcohol	100	109
Tert Butyl Alcohol	100	278
Caprolactum	5	91
Cresols	5	5
Cresylic Acid	5	16
Cumene	50	139
Cyclohexane	300	699
Dicyclopentadiene	5	14
Diethylene Triamine	1	2
Ethanolamine	3	4
Ethyl Benzene	100	139
Ethylene Glycol Monoethyl Ether	50	36
Ethylene Glycol Monomethyl Ether	25	56
Furfural Alcohol	10	9
Glutaraldehyde	0.2	154
Gasoline	300	1725
Iso Hexane	500	1598
n-Hexane	50	881
Iso Phorone	5	3
Methyl Acetate	200	1543
Methyl Alcohol	200	908
Methyl Isobutyl Carbinol	25	34
Methol Isobutyl Ketone	50	91
Methyl Ethyl Ketone	200	908
Iso Octyl Alcohol	50	28
Pentane	600	3913
Iso Propyl Acetate	250	431
N Propyl Acetate	200	227
Iso Propyl Alcohol	400	300
N Propyl Alcohol	200	132
Styrene	50	54
Toluene	100	200
1,1,1 Tricholoroethane	350	908
Vinyl Acetate	10	817
M Xylene	100	54
P Xylene	100	59
Ethyl Acetate	400	661

The top-off gauging scenario is summarized below in Table V-3.

TABLE V-3.   TANK TOP-OFF GAUGING SCENARIO

Tank No.	Time at Beginning of Topoff	Total Gauging Time (min)	Elapsed Time Between Adjacent Topoffs (min)
1	0756:40	2.7	5.2
2	0804:30	18.5	28.5
3	0851:30	18.5	47
4	0957	13	3
5	1013	21.9	7.1
6	1042	4	

The total duration of the scenario is roughly 2.75 hours.

The chemical contents of the six tanks were selected for the tank top-off scenario from the products in Table V-2 and are shown in Table V-4.

It is interesting to note that these six chemicals, which passed the screening process, have previously been identified as chemicals that may result in toxicological interactions (1).

TABLE V-4.   CHEMICALS IN TANK TOP-OFF SCENARIO

Tank No.	Chemical	C_e* (ppm)
1	Methyl ethyl ketone	900
2	Acetone	1600
3	Toluene	200
4	Methyl isobutyl ketone	90
5	n-Hexane	900
6	Ethyl acetate	700

Tier I Evaluations.   The tank top-off work scenario described above involves the sequential exposure of a crewman to the following chemicals at the specified average concentrations (rounded to two significant figures) and for the designated durations: metyl ethyl ketone (MEK), 900 ppm, 2.7 min;

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acetone (ACT), 1600 ppm, 18.5 min; toluene (TOL), 200 ppm, 18.5 min; methyl isobutyl ketone (MIK), 90 ppm, 13 min; n-hexane (HXA), 900 ppm, 21.9 min; and ethyl acetate (ETA), 700 ppm, 4 min. The time intervals between exposures to these chemicals during successive top-off activities range from three minutes to 47 minutes. The exposure data and other information relevant to a toxicological assessment of the exposures are summarized in Table V-5.

During tank top-off of each of the six tanks, the concentration of vapor of each chemical exceeds 50 percent of the TLV-TWA value for the chemical and meets the criterion of a medical monitoring response level. In fact, the concentrations exceed even the TLV-TWA values. Furthermore, because the crewman performing the top-off activities is exposed sequentially within a 3-hour period to six chemicals that act on the same organ system, the total exposure should be evaluated toxicologically as an exposure to a mixture of the chemicals. Using the ACGIH additive formula to evaluate the mixture, concentrations of chemicals in the combined exposure exceed 50 percent of the TLV-TWA value for the mixture and meet the criterion of a medical monitoring response level. An in-depth toxicological assessment of the exposure sequence is presented in the next section.

Tier II Evaluations. The toxic effects of acute exposures to toluene (TOL) and methyl isobutyl ketone (MIK) were reviewed previously in Section IV.3.1. Both chemicals are irritants and, at higher concentrations, are central nervous system depressants. At the predicted concentration of 90 ppm of MIK, an exposure of 13 minutes may produce irritation of the eye and respiratory tract as well as other effects such as headache, nausea, impaired judgement, dizziness and gastrointestinal disturbances. Similarly, toxic effects that may be anticipated from an 18.5-minute exposure to 200 ppm of TOL include eye and throat irritation and, possibly, central nervous system effects such as headache, lassitude, fatigue and slowed reflexes. These symptoms have been reported in humans exposed to comparable concentrations, although for longer periods of time (human short exposure data for TOL are limited).

Methyl ethyl ketone (MEK) is also an irritant and, at high atmospheric concentrations, may depress the central nervous system. Prolonged

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TABLE V-5. PREDICTED EXPOSURES TO SELECTED CHEMICALS DURING OPEN TANK GAUGING

Sequence No.	Pers. Des.	Chemical	Chem. Abr.	Duration (min)	Exposure Concentration (ppm)*	TLV-TWA (ppm)	TLV-STEL (ppm)	TLV-C (ppm)	Toxicological Significance**
1	A	Methyl ethyl ketone	MEK	2.7	900	200	300	--	MMRL
	A	Acetone	ACT	18.5	1600	750	1000	--	MMRL
	A	Toluene (Skin)	TOL	18.5	200	100	150	--	MMRL
	A	Methyl isobutyl ketone	MIK	13	90	50	75	--	MMRL
	A	n-Hexane	HXA	21.9	900	50	--	--	MMRL
	A	Ethyl acetate	ETA	4	700	400	--	--	MMRL

MMRL*** (brace spanning Toxicological Significance column)

* Concentration rounded to two significant figures

** MMRL = Exposure meets criterion of medical monitoring response level.

*** MMRL = Exposure meets criterion of medical monitoring response level when ACGIH additive formula is used to evaluate the mixture of chemicals.

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skin contact may defat the skin and produce dermatitis. MEK is considered to have a low order of toxicity following both acute and chronic exposures but the vapors are slightly more irritating to the mucous membranes and conjunctiva than acetone (2). Nelson et al. (2) determined sensory thresholds in ten volunteers exposed for three to five minutes to MEK. Exposures to 25 ppm for five minutes were without untoward effects. Exposures to 100 ppm gave an identifiable odor and produced mild irritation of the nose and throat. Concentrations of 200 ppm for 15 minutes produced complaints of irritation of the nose and throat and a strong odor. At a concentration of 300 ppm, MEK was found to objectionable and, at concentrations greater than 300 ppm, irritation of the eyes, nose and throat and nausea were seen, particularly, in unacclimatized subjects. In workers exposed to 300 to 500 ppm of MEK, Elkins (2) reported comr'aints of headache, irritation and nausea. Therefore, the exposure of a crewman to 900 ppm of MEK in this sequence has the potential of irritating the eyes, nose and throat and of producing headache, nausea and other central nervous system effects. However, the likelihood of marked effects is reduced considerably by the short exposure of 2.7 minutes.

Prolonged exposures to methyl ehtyl ketone (MEK) have been reported to produce both central and peripheral nervous system effects (2). In one study, exposure to vapor concentrations of 90 to 270 ppm MEK for 4 hours shortened time estimations in men and increased the variation in time estimation tests in women. Workers exposed via inhalation to vapor concentrations of 300 to 600 ppm and by skin contact complained of numbness in the upper extremities. MEK has also been implicated in occupational polyneuropathies in shoe workers and in Swedish steel workers. Direct evidence that MEK by itself produces neuropathies is lacking (2). However, there is evidence that MEK may interact with methyl n-butyl ketone (MBK), toluene (TOL) or n-hexane (HXA) to shorten the onset of neuropathies produced by the latter chemicals and may predispose the liver to injury from hepatotoxins such as carbon tetrachloride and chloroform (3-5).

Acetone (ACT) is also irritating and exposure to high concentrations may produce central nervous system depression and narcosis. Prolonged or repeated skin contact may defat the skin and produce dermatitis. As a result of human experience and experimental studies, ACT is considered to be

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one of the least toxic solvents used in industry. Nelson et al. (2) reported that concentrations of ACT below 500 ppm were without effect and that 500 ppm produced eye and nasal irritation in unacclimatized volunteers. In another study by Matsushita et al. (2), groups of five students were exposed to 0, 100, 250, 500 or 1000 ppm ACT vapor for six hours. Irritation of the eyes, nose and throat was noted at 500 and 1000 ppm. Similar findings were reported by Raleigh and McGee (2), except that the threshold effect concentration was somewhat higher. These investigators surveyed workers exposed for eight hours per day to an average atmospheric concentration of ACT of 1006 ppm. Eye irritation was transient and generally occurred at concentrations above 1000 ppm. There was no indication of central nervous system effects at these levels. The investigators concluded that 1000 ppm ACT produced no untoward effects, with the exception of slight transient irritation of the eyes, nose and throat. The results of these and other studies indicate that central nervous system depression and narcosis would not be produced by ACT until concentrations approach or exceed 10,000 ppm (2). The IDLH level of 20,000 ppm designated for ACT is consistent with these results.

Based on the results of human experimental studies and industrial exposures to acetone (ACT), the 18.5-minute exposure to 1600 ppm ACT during open gauging of Tank No. 2 is unlikely to produce more than irritation to the eyes, nose and throat. However, this exposure to ACT is only one of a sequence of exposures to six different chemicals with irritant and CNS depressant effects and biological interactions between some of these chemicals have been reported. With ACT, results of studies of human industrial exposures and of experimental studies in animals suggest potential interactions between this chemical and ethyl alcohol (EAL), methyl ethyl ketone (MEK) and a number of aliphatic acetates (4, 6-8).

During open tank gauging of Tank No. 5, the predicted exposure of the crewman is to 900 ppm of n-hexane (HXA) for 21.9 minutes. Although this concentration is severalfold greater than the TLV-TWA value of 50 ppm, HXA is not considered a highly toxic chemical in acute exposures. The acute toxicity of HXA was reviewed in Section IV.3.1. At the concentration predicted for this sequence, the principal toxic effects that may be anticipated are eye and upper respiratory tract irritation, headache and nausea. Eye and

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throat irritation were reported following human exposure to 880 ppm HXA for 15 minutes (9); in another study, headache and nausea, in addition to eye and throat irritation, were observed after an exposure to 2000 ppm for 10 minutes (10).

In recent years, attention has been focused on the severe toxic effects that may result from chronic exposures to hexane (HXA). Since 1967, there has been a number of reports of polyneuritis and polyneuropathy in industrial workers exposed to HXA. Apparently, peripheral neuropathies have resulted from exposures to HXA at concentrations as low as 500 ppm and even possibly lower (10). These effects have been attributed principally to the neurotoxic metabolite of HXA, 2,5-hexanedione, which is also a metabolite of methy n-butyl ketone (9). There is also evidence of potential biological interactions between HXA and other chemicals. For example, Spencer et al. (10) and Altenkirch et al. (11) reported that concurrent exposure to MEK or possibly other chemicals or drugs which induce the liver oxidative mechanism reduces the time for neuropathy to appear as a result of exposure to HXA.

The last exposure of the crewman in this sequence is a 4-minute exposure to a predicted concentration of 700 ppm of ethyl acetate (ETA) during open gauging of Tank No. 6. Ethyl acetate is an irritant and the predicted concentration is sufficiently high to produce mild toxic effects and symptoms. In a study with human unacclimatized volunteers, the volunteers found vapors of ETA mildly irritating to the eyes, nose and throat at 400 ppm (10). Although severe irritation from a short exposure to 700 ppm ETA is not anticipated, it should be noted that the effects of ETA could be potentiated by the previous exposures to the other five irritating chemicals.

In summary, this tank top-off work scenario results in the sequential exposures of a crewman to the vapors of six chemicals, all of which are irritants and have potential central nervous system effects. When evaluated as individual exposures, the concentration of chemical in each of the six exposures exceeds 50 percent of the TLV-TWA value for the chemical and meets the criterion of a medical monitoring response level. In view of the short intervening times between exposures, the sequence may be regarded as a simultaneous exposure to the six chemicals. The exposure also exceeds the TLV-TWA

for the mixture. At the predicted concentration and duration, the exposure to each chemical is likely to produce some degree of eye and upper respiratory tract irritation and, in the case of toluene (TOL), methyl ethyl ketone (MEK) and hexane (HXA), possibly some mild central nervous system effects. However, because of potential biological interactions among these chemicals, a toxico- logical assessment based on toxic effects anticipated at the concentrations of individual chemicals may be overly conservative and, possibly, very inaccur- ate. Potentiation of effects resulting from additive or synergistic inter- actions cou'd produce irritation, central nervous system depression and other effects of much greater severity than might be anticipated. Although indus- trial exposures and animal studies indicate that some interactions among the six chemicals do occur, data are insufficient to enable the prediction of toxic effects and symptoms that would result from the exposures to the chemi- cal vapors in this tank top-off scenario.

V.3.2   Deck Work Downwind of Loading Tanks

During the initial stages of product loading, the concentration of the vapors that are discharged from a clean tank is relatively low. As loading proceeds, the discharge concentration increases, and at tank top-off the vapor concentration may approach or equal the saturated concentration corresponding to the temperature of the chemical. Throughout the loading, product vapors are diluted and disbursed as they are transported downwind of the vent.

Crew members working on deck during loading may be exposed to these vented vapors even though they are at a considerable distance from the vent. For example, a crew member who mans a product delivery valve during the final stages of loading may be at a distance from the vent source, but his work station may be totally within the boundaries of the downwind vapor plume. Similarly, crew members may actively traverse the vapor plumes during activities such as loading of ship's stores, retrieving of equipment from an aft locker for use in the forward part of the ship, walking to and from the deckhouse or other activities.

The downwind vapor plume concentrations are a function of the chemical and its properties, vent height, wind speed and product loading rate. The potential for downwind contact with and meaningful exposure to the vapor plume is greatest during the latter stages of loading when vent concentrations are maximum.

The purpose of this section is to present and interpret predicted exposures of crew members who may work downwind of a vapor vent. The predicted exposures were based on an analytical plume dispersion model, ONDEK, which was developed and validated as a part of this overall project. Model documentation appears in the Southwest Research Final Report Project No. 06-5686 (1). The computer model was used to predict downwind vapor concentration at breathing zone height above the deck for 11 chemicals and combinations of vent height, wind speed and loading rate. For each chemical, a saturated vapor concentration at the vent was assumed. This condition corresponds to the final stages of a tank loading. The exposure concentration was taken to be the predicted level at 20 m downwind of the vent and at man breathing height (approximately 1.7 m). The duration of the exposure was assumed to include the last 15 minutes of loading. The concentration at 20 m downwind was assumed to represent an average exposure level. It recognizes that a crew member may walk through regions of the plume that have lower concentrations as well as areas that are at higher concentrations. The model predictions also indicate the parametric effects of wind speed, loading rate and vent height on exposure levels.

Tier I Evaluations. The pertinent data for a Tier I toxicological assessment of the predicted exposures to a crewman to each of 11 chemicals during deck work downwind of loading tanks are summarized in Table V-6. For each chemical, there are four exposure sequences which differ in predicted average and maximum vapor concentrations because of different assumed wind speeds or loading rates. Thus, there are 44 separate exposure sequences shown in the table. Each sequence is considered separately to determine whether the concentration of chemical in an exposure meets the criterion of a medical monitoring response level; sequences are not combined for evaluation. For each sequence, the assumption is made that the crewman is exposed to the predicted average concentration of chemical at 20 meters downwind of the vent

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TABLE V-6.   PREDICTED EXPOSURE TO SELECTED CHEMICALS DURING DECK WORK DOWNWIND OF LOADING TANKS

Sequence No.	Chemical	Chem. Abbr.	Vent Height (m)	Wind Speed (m/s)	Loading Rate (m³/hr)	Average Exposure Conc. at 20 m, (ppm)*	Max. Conc. at Man Br. Height (ppm)	TLV-TWA (ppm)	TLV-STEL (ppm)	TLV-C (ppm)	Toxicological Significance/** Comments
1	n-Hexane	HXA	1	1.12	159	29	5,000	50	--	--	MMRL
2	n-Hexane	HXA	1	1.12	318	130	28,000	50	--	--	MMRL
3	n-Hexane	HXA	1	2.24	159	29	2,200	50	--	--	MMRL
4	n-Hexane	HXA	1	2.24	318	59	5,100	50	--	--	MMRL
5	Methyl ethyl ketone	MEK	1	1.12	159	61	5,200	200	300	--	NIS
6	Methyl ethyl ketone	MEK	1	1.12	318	130	28,000	200	300	--	MMRL
7	Methyl ethyl ketone	MEK	1	2.24	159	30	2,300	200	300	--	NIS
8	Methyl ethyl ketone	MEK	1	2.24	318	61	5,300	200	300	--	NIS
9	Toluene	TOL	1	1.12	159	17	1,500	100	150	--	NIS
10	Toluene	TOL	1	1.12	318	37	7,600	100	150	--	NIS
11	Toluene	TOL	1	2.24	159	8.3	650	100	150	--	NIS
12	Toluene	TOL	1	2.24	318	17	1,500	100	150	--	NIS
13	Methyl acetate	MTT	1	1.12	159	100	8,600	200	250	--	MMRL
14	Methyl acetate	MTT	1	1.12	318	230	30,000	200	250	--	MMRL
15	Methyl acetate	MTT	1	2.24	159	51	3,900	200	250	--	NIS
16	Methyl acetate	MTT	1	2.24	318	100	8,900	200	250	--	MMRL
17	Ethylidene norbornene	ENB	1	1.12	159	2.8	250	5	--	5	MMRL
18	Ethylidene norbornene	ENB	1	1.12	318	6.1	1,200	5	--	5	MMRL
19	Ethylidene norbornene	ENB	1	2.24	159	1.3	100	5	--	5	NIS
20	Ethylidene norbornene	ENB	1	2.24	318	2.8	250	5	--	5	MMRL
21	Carbon tetrachloride (skin)	CBT	6	1.12	159	34	37	5	20	--	MMRL
22	Carbon tetrachloride (")	CBT	6	1.12	318	54	55	5	20	--	MMRL
23	Carbon tetrachloride (")	CBT	6	2.24	159	18	20	5	20	--	MMRL
24	Carbon tetrachloride (")	CBT	6	2.24	318	33	35	5	20	--	MMRL
25	Benzene	BNZ	6	1.12	159	27	29	10	25	--	MMRL
26	Benzene	BNZ	6	1.12	318	43	44	10	25	--	MMRL
27	Benzene	BNZ	6	2.24	159	15	17	10	25	--	MMRL
28	Benzene	BNZ	6	2.24	318	27	29	10	25	--	MMRL
29	Chloroform	CHF	6	1.12	159	58	64	10	50	--	MMRL
30	Chloroform	CHF	6	1.12	318	93	95	10	50	--	MMRL
31	Chloroform	CHF	6	2.24	159	31	34	10	50	--	MMRL
32	Chloroform	CHF	6	2.24	318	55	59	10	50	--	MMRL
33	Ethylene chlorohydrin (skin)	ECH	6	1.12	159	37	40	1	--	1	MMRL
34	Ethylene chlorohydrin (skin)	ECH	6	1.12	318	58	59	1	--	1	MMRL
35	Ethylene chlorohydrin (skin)	ECH	6	2.24	159	20	22	1	--	1	MMRL
36	Ethylene chlorohydrin (skin)	ECH	6	2.24	318	36	39	1	--	1	MMRL
37	Epichlorohydrin (skin)	EPC	6	1.12	159	4.5	4.8	2	5	--	MMRL
38	Epichlorohydrin (skin)	EPC	6	1.12	318	7.1	7.2	2	5	--	MMRL
39	Epichlorohydrin (skin)	EPC	6	2.24	159	2.5	2.8	2	5	--	MMRL
40	Epichlorohydrin (skin)	EPC	6	2.24	318	4.4	4.8	2	5	--	MMRL
41	Vinyl acetate	VAM	4	1.12	159	47	86	10	20	--	MMRL
42	Vinyl acetate	VAM	4	1.12	318	77	110	10	20	--	MMRL
43	Vinyl acetate	VAM	4	2.24	159	25	34	10	20	--	MMRL
44	Vinyl acetate	VAM	4	2.24	318	46	84	10	20	--	MMRL

* Average exposure concentration during last 15 minutes of loading.

** MMRL = Exposure meets criterion of medical monitoring response level.

NIS - Not of toxicological significance because exposure concentration is below medical monitoring response level.

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during the last 15 minutes of tank loading. During the 15 minutes, the crew-
man may be exposed to considerably higher concentrations of chemical vapors as
he walks through the vapor plume. These are probably very brief excursions in
exposure concentration and are not considered in the Tier I evaluations, but
are addressed in the Tier II evaluations of exposures.

Of the 44 exposure sequences, the concentrations of chemicals in
only nine sequences (Sequence Nos. 5, 7, 8, 9-12, 15 and 19) do not equal or
exceed 50 percent of the TLV-TWA values for the chemicals. These exposures do
not meet the criterion of a medical monitoring response level and are not
discussed further. In the other 35 exposure sequences, the atmospheric con-
centrations of chemicals equal or exceed 50 percent of the TLV-TWA values and
meet the criterion of a medical monitoring response level. In these
sequences, the crewman is exposed to n-hexane (HXA) in Sequence Nos. 1, 2, 3
and 4, methyl ethyl ketone (MEK) in Sequence No. 6; methyl acetate (MTT) in
Sequence Nos. 13, 14 and 16; ethylidene norbornene (ENB) in Sequence Nos. 17,
18 and 20; carbon tetrachloride (CBT) in Sequence Nos. 21, 22, 23 and 24;
benzene (BNZ) in Sequence Nos. 25, 26, 27 and 28; chloroform (CRF) in Sequence
Nos. 29, 30, 31 and 32; ethylene chlorohydrin (ECH) in Sequence Nos. 33, 34,
35 and 36; epichlorohydrin (EPC) in Sequence Nos. 37, 38, 39 and 40; and vinyl
acetate (VAM) in Sequence Nos. 41, 42, 43 and 44. An in-depth toxicological
assessment of each of these 35 exposure sequences is presented in the Tier II
evaluations.

Tier II Evaluations. In the sequences involving loading of
hexane (HXA), the predicted average concentrations of vapors range from 28.7
to 131 ppm. The acute inhalation toxicity of HXA was reviewed in Section
IV.3.1. From a review of the scientific literature, it appears that short
exposures to concentrations less than 500 ppm do not cause adverse effects.
Exposure concentrations between approximately 800 to 1500 ppm may produce
irritation of the eyes and upper respiratory tract as well as headache and
nausea. Thus, the predicted average concentrations in these sequences are
unlikely to produce any adverse effects or symptoms. However, potential
maximum concentrations in the vapor plume are very high. For example, the
predicted maximum concentration for HXA in Sequence No. 2 is 27,800 ppm, which
considerably exceeds the IDLH value of 5000 ppm for HXA. At the predicted

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maximum concentration, the chemical is highly irritating and, of more impor-
tance, central nervous system effects would be very marked, if sufficient
vapor were inhaled. For example, an exposure to only 5000 ppm of HXA has been
reported to cause dizziness and a sense of giddiness (10). It is probably
unlikely that a crewman would remain in a highly irritating area of the plume
for sufficiently long to be incapacitated or suffer irreversible damage.
However, the possibility exists and precautions should be taken.

During the loading of a tank with methyl ethyl ketone (MEK)
under different assumed wind speeds and loading rates, the predicted average
concentration of vapor (134 ppm) in one sequence (Sequence No. 6) exceeds 50
percent of the TLV-TWA value (200 ppm) and meets the criterion of a medical
monitoring response level. The acute and chronic inhalation toxicities of MEK
were reviewed in Section V.3.1. Methyl ethyl ketone is considered to have a
low order of toxicity following both acute and chronic exposures. However,
short exposures to 100 ppm have been reported to produce mild irritation of
the nose and throat. Headache, irritation and nausea were experienced after
exposures to 300 to 500 ppm. Based on these reports, it is likely that a 15-
minute exposure to 134 ppm in Sequence No. 6 would produce only mild irrita-
tion of the upper respiratory tract. Although potential maximum concen-
trations of MEK in the vapor plumes during three loading sequences (Sequence
Nos. 5, 6 and 8) exceed the IDLH value of 3000 ppm and are sufficiently high
to cause central nervous system depressant effects, it is unlikely that a
crewman would remain in this irritating atmosphere for more than a very brief
time.

During loading of a methyl acetate (MTT) tank, the predicted
average concentrations at 20 meters from the vent in Sequence Nos. 14, 15 and
17 range are 104, 229 and 104 ppm, respectively. Each of these concentrations
exceeds 50 percent of the TLV-TWA (200 ppm) for the chemical and meets the
criterion of a medical monitoring response level. Methyl acetate is an irri-
tant and has also been reported to cause ocular and nervous disturbances in
workers exposed to the vapor (10). Inflammation of the mucous membranes of
the eyes and respiratory passages, nervous irritation and tightness of the
chest are among the effects observed. It was suggested by Henderson and
Haggard (10) that methanol formed by hydrolysis in the body might be respon-

sible for the toxicity of MTT. No cases of irritation or systemic injury have been reported from exposures below 200 ppm; for this reason, the ACGIH recommended a TLV-TWA of 200 ppm and a TLV-STEL of 250 ppm for MTT. However, Cook (10) recommended that workers exposed to concentrations of MTT exceeding 100 ppm should be under medical observation. In Sequence Nos. 13 and 16, the exposures are unlikely to produce more than slight irritation of the eyes. In Sequence No. 14, the predicted concentration of 229 ppm of MTT could produce moderate irritation of the eyes and respiratory tract. The predicted maximum concentrations of MTT in all four sequences involving loading of the tank of MTT are sufficiently large to cause severe toxic effects and symptoms. In fact, in Sequence No. 14, the predicted maximum concentration of 50,000 ppm is fivefold the IDLH value of 10,000 ppm for MTT. However, it is unlikely that a worker would remain in the highly irritating areas of the vapor plumes for more than a very brief time in these sequences.

In the next tank loading scenario involving ethylidene norbornene (ENB), the predicted average concentrations of vapor in Sequence Nos. 17, 18 and 20 are 2.8, 6.1 and 2.8 ppm, respectively. Each of these concentrations exceeds 50 percent of the TLV-TWA value of 5 ppm (which is also a ceiling limit) for ENB and meets the criterion of a medical monitoring response level. In Sequence No. 18, the predicted average concentration of 6.1 ppm exceeds this ceiling limit value. Ethylidene norbornene is an irritant; however, a variety of effects, including testicular atrophy, hepatic lesions and slight blood changes, have been reported in chronically exposed animals (10). Human exposure data are limited but, in one important study, human volunteers who were exposed to ENB vapors experienced some irritation of the eyes and nose in 30-minute exposures at 11 ppm and transient eye irritation at 6 ppm (10). Therefore, minimum toxic effects would be anticipated from exposure to the predicted concentrations of ENB of 2.8 ppm in Sequence Nos. 17 and 20. In Sequence No. 18, in which the predicted average concentration is 6.1 ppm, the exposure might result in mild irritation of the eyes. In other areas of the plumes in which predicted maximum concentrations in Sequence Nos. 17, 18, 19 and 20 range from 104 to 1190 ppm, exposures would be extremely irritating to the eyes and respiratory tract and could cause severe toxic effects if the crewman remained in the area of the plume.

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In Sequence Nos. 21, 22, 23 and 24, the predicted average concentrations of carbon tetrachloride (CBT) during tank loading range from 18.1 to 54.0 ppm. The concentration of vapor in each of these four sequences exceeds 50 percent of the TLV-TWA value (5 ppm) and meets the criterion of a medical monitoring response level. In three of these sequences (Sequence Nos. 21, 22 and 24), the concentrations exceed even the TLV-STEL value (20 ppm). Predicted maximum concentrations in the vapor plumes range from 20.3 to 54.8 ppm. The toxicity of CBT was reviewed previously in Section IV.3.3. In reports of acute industrial exposures to CBT, workers exposed to 33 to 124 ppm experienced fatigue, and other workers exposed to 45 to 97 ppm exerienced headaches and giddiness. Because of these reports, 20 ppm was adopted as the TLV-STEL by the ACGIH to avoid the occurrence of fatigue and other central nervous system symptoms in workers. Therefore, it is possible that fatigue, headaches and mild CNS effects would occur in marine workers exposed to the predicted average and maximum concentrations in these four sequences. In addition, as noted previously, CBT is a suspect human carcinogen and exposures to all such agents should be avoided.

In the four sequences (Sequence Nos. 25, 26, 27 and 28) during which tanks are loaded with benzene (BNZ), prediced average concentrations range from 15 to 42.9 ppm. Each of the four concentrations exceeds 50 percent of the TLV-TWA value (10 ppm) for BNZ and meets the criterion of a medical monitoring response level. In fact, each concentration exceeds the TLV-TWA value and, in three of the four sequences, the concentration also exceeds the TLV-STEL value (25 ppm). Thus, exposures to the predicted average concentrations of BNZ during deck work downwind of tank loading under all of the assumed conditions of wind speed and loading rate are potentially hazardous exposures. The acute inhalation toxicity of BNZ was reviewed in Section IV.3.2. The primary symptoms that may result from acute inhalation of this chemical are due to its effects on the central nervous system. Inhalation of concentrations of up to 25 ppm has been reported to be without effects but exposure to 50 to 150 ppm may produce headache, lassitude and weariness (12). Thus, single exposures to the predicted average concentrations or to the predicted maximum concentrations (16.8 to 43.5 ppm) are unlikely to cause symptoms other than headache and other mild central nervous system effects. However, repeated exposures to these concentrations over a prolonged period of

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time could possibly cause a variety of pathological conditions (hematologic and myelotoxic effects, CNS disorders) which were reviewed in detail in Section IV.3.2. In addition, BNZ has been designated a suspect carcinogen for man because of a reported higher incidence of leukemia in certain types of industrial workers who were chronically exposed to this chemical. Therefore, although single exposures may not produce severe effects, all exposures to BNZ should be avoided in view of the seriousness of potential effects from chronic repeated exposures.

In Sequence Nos. 29, 30, 31 and 32, predicted average and maximum concentrations during deck work downwind of loading of a tank of chloroform (CRF) range from 30.5 to 93.2 ppm and from 34.4 to 95.0 ppm, respectively. In each of these sequences, the average concentration exceeds 50 percent of the TLV-TWA value (10 ppm) for this chemical and meets the criterion of a medical monitoring response level. In three of these sequences (Sequence Nos. 29, 30 and 32), the concentrations exceed the TLV-STEL value (50 ppm). The toxicity of CRF was reviewed in Section IV.3.1. The primary effects of acute inhalation of CRF are due to its depressant action on the central nervous system but even higher concentrations of CRF than of BNZ are necessary to cause symptoms. For example, it has been reported that man can tolerate an exposure of 389 ppm of CRF for 30 minutes without any ill effects and that an exposure of approximately 1000 ppm will produce dizziness, intracranial pressure and nausea after 7 minutes (13). Thus, literature data suggest that the single 15-minute exposures to the predicted average concentrations, and even to the predicted maximum concentrations, in these four sequences are unlikely to produce toxic effects or symptoms. However, repeated exposures to these concentrations over prolonged periods of time are of concern because of possible liver and kidney injury from chronic exposure to this chemical and because CRF has been identified as a suspect carcinogen in man. In view of the potential seriousness of these effects, exposures to CRF and to other suspect carcinogens should be avoided.

During loading of tanks with ethylene chlorohydrin (ECH), predicted average concentrations in the four sequences (Sequence Nos. 33, 34, 35 and 36) range from 20.0 to 58.0 ppm and predicted maximum concentrations range from 22.4 to 58.8 ppm. The predicted average (and maximum) concentrations

exceed 50 percent of the TLV-TWA value of 1 ppm (which is also a ceiling limit value) and meet the criterion of a medical monitoring response level. Ethylene chlorohydrin is a highly toxic chemical which acts on several target organs and produces a variety of toxic effects. Sites of biological actions and toxic effects include: 1) central nervous system (respiratory depression, paralysis, mental disturbances, brain damage); 2) cardiovascular system (myocardiopathy, sinus tachycardia, circulatory shock); 3) liver (glutathione depletion, inactivation of drug-metabolizing enzymes, degeneration); 5) gastrointestinal (nausea, vomiting, epigastric pain); 6) skin (erythema, blisters); 7) eyes (irritation); and, 8) mutagen (10). Acute toxicity may be manifested by respiratory depression and death without specific organ pathology. Precise human exposure data relevant to ECH are not available. Dierker and Brown (10) reported a fatal case of ECH poisoning in man that resulted from a two-hour exposure to an estimated concentration of 300 ppm. Bush et al. (10) described one fatal and several non-fatal cases of ECH poisoning in industrial workers. Autopsies showed severe damage to the liver and brain and changes in many other organs. Exposure concentrations were estimated at between 300 and 500 ppm. In animal studies, deaths and toxic effects have been reported at much lower concentrations. For example, Ambrose (10) reported that a single one-hour exposure to 7.5 ppm and repeated one-hour exposures to 2 ppm were fatal to rats; however, these results are inconclusive since the concentrations of ECH were not measured. Because of the potentially serious systemic toxicity of ECH, a ceiling limit of 1 ppm was adopted by the ACGIH. Predicted average and maximum concentrations of ECH in the four sequences considerably exceed this ceiling limit value and could cause serious systemic toxic effects. Every precaution should be taken by marine workers to avoid exposure to this chemical.

Epichlorohydrin (EPC) is also a highly toxic chemical, with a TLV-TWA of 2 ppm and a TLV-STEL of 5 ppm. It is irritating to the eyes and respiratory tract and also is systemically toxic by the oral, percutaneous, subcutaneous and respiratory routes. In animal studies, deaths have been attributed to effects on the central nervous system and the respiratory tract from high doses (10). Symptoms developed very slowly, with several days elapsing between marked respiratory depression and death. In rats, Gage (10) reported that six-hour exposures at 120 ppm caused lung, liver and kidney

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injury, at 56 ppm produced respiratory distress and at 9 ppm no effects were observed. Human exposure data are limited but there are reports of lung edema and kidney lesions in men exposed briefly at concentrations in excess of 100 ppm and burning of the eyes and nasal mucosa at 20 ppm. Other reported effects in man are nausea, dyspnea, bronchitis and enlarged liver. Predicted average concentrations of EPC during tank loading under the conditions of Sequence Nos. 37, 38, 39 and 40 range from 2.5 to 4.5 ppm, with predicted maximum concentrations of from 2.8 to 7.2 ppm. The predicted average concentrations in all four sequences exceed 50 percent of the TLV-TWA value for EPC and meet the criterion of a medical monitoring response level. The predicted average concentration in Sequence No. 38 also exceeds the TLV-STEL value. Based on the limited human exposure data reported in the literature, the exposures in these sequences may cause irritation of the eyes and respiratory tract but severe systemic effects are not anticipated.

During loading of vinyl acetate (VAM), predicted average concentrations of the chemical range from 24.8 to 77.2 ppm in the four loading sequences. Each of the concentrations exceeds 50 percent of the TLV-TWA value of 10 ppm and meets the criterion of a medical monitoring response level. In fact, each of these concentrations exceeds the TLV-TWA value as well as the TLV-STEL value of 20 ppm. Anticipated toxic effects from these exposures include eye and upper respiratory tract irritation. These effects could be considerably more severe in exposures to the predicted maximum concentrations, which range from 54.2 to 106 ppm. In a study of of 21 chemical operators exposeed to VAM at levels of 5 to 10 ppm, it was reported that the chemical is not a significant upper respiratory tract irritant at 10 ppm (10). At approximately 22 ppm, slight irritation in the form of cough and hoarseness was observed. Medical records and multiphasic examinations revealed no evidence of chronic affects from daily exposures to 5 to 10 ppm.

V.3.3 Tank Entry

In Section IV.1 measured exposure data during tank entry were presented and evaluated. The purpose of this section is to present and evaluate predicted tank entry exposure data for chemicals other than those that were monitored in the field. The predicted exposures were based on two

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analytical tank ventilation models (TANKM AND TANKP) that were developed and validated as a part of this overall project. Documentation of the models appears in the Southwest Research Institute Project No. 06-5686 Final Report (1). The tank cleaning, ventilation and work scenarios will be described later.

The chemicals that were used in the model predictions were selected from the list of products in Table V-2. These chemicals were rearranged in order of increasing solubility in water from insoluble to infinitely soluble. The appropriate TLV-TWAs were also catalogued. The solubility values fell into four natural ranges:

°   Solubility of zero to 9.5 mg/L

°   Solubility from 50 to 515 mg/L

°   Solubility from 4400 to 25000 mg/L

°   Solubility greater than 77000 mg/L

Two chemicals with different TLVs were selected from each solubility grouping. The chemicals, solubilities and TLVs of the selected chemicals are summarized in Table V-7.

TABLE V-7. CHEMICALS SELECTED FOR TANK CLEANING AND ENTRY SCENARIOS

Chemical	Solubility (mg/L)	TLV-TWA (ppm)
1,2,4 Trichlorobenzene	insoluble	5
n-Hexane	9.5	50
Ethyl benzene	152	100
Styrene	300	50
1,1,1 Trichloroethane	4,400	350
Methyl isobutyl carbinol	17,000	25
Methyl acetate	319,000	200
Ethanolamine	infinite	3

The important assumptions of the tank cleaning and entry scenario that are common to all model predictions are as follows:

°   The tank is ventilated for 90 minutes prior to man entry;

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° In-tank work time is 30 minutes;

° Tank dimensions are constant and independent of chemical;

° Initial vapor concentration at the beginning of ventilation is 10 percent of the saturated vapor concentration at 20°C;

° The ventilation process is isothermal at 20°C;

° The thickness of the residual liquid layer on the tank bottom is 1.0 cm at the beginning of ventilation;

° Ventilation flow rate is constant for all chemicals;

° The tank is ventilated during man entry.

Because of the negligible solubility of the first two chemicals, exposures for these chemicals were predicted using the TANKP model. This model assumes that the tank is not washed prior to ventilation; the residual liquid layer is pure chemical which evaporates during forced ventilation. Exposure prediction for the last six chemicals made use of the TANKM model. This model assumes that tank has been washed prior to ventilation, and the residual liquid layer is a binary mixture of a chemical in water. The chemical evaporates from solution during ventilation. For ethyl benzene through methyl acetate, the initial chemical concentration in solution at the beginning of ventilation was set equal to one-half of the solubility limit. For ethanolamine, the initial solute concentration was set equal to the initial concentration of methyl acetate in water (an assumption based on the infinite solubility of ethanolamine). Both models predict the vapor concentration-time history within the tank from the beginning of ventilation and throughout the in-tank work time. The computer code output includes instantaneous and integrated average vapor concentrations during tank entry. These outputs together with the exposure duration were the inputs to the toxicological assessment.

The following qualitative description of the model predictions will complement the subsequent toxicological interpretations. Collectively, the predicted concentration-time profiles exhibited three classes of response.

Class I. This response class included the concentration-time profiles for hexane and trichlorobenzene. The gas freeing process for both of these products involved evaporation of a pure chemical residue layer on the tank bottom. In both cases, the tank vapor concentration reached a steady-state value above the initial concentration at the beginning of ventilation. the steady-state vapor concentration coincides with a constant chemical evaporation rate. As trichlorobenzene is a low vapor pressure chemical, all of the residual layer did not evaporate before the time of tank entry. Consequently, entry occurred during the steady-state evaporation period where vapor levels were in excess of the TLV. For hexane, which has a much higher vapor pressure, the chemical layer completely evaporated prior to tank entry. However, the ventilation times between cessation of evaporation and entry was insufficient to gas free the tank below the TLV.

Class II. This response class included the concentration-time profiles for ethyl benzene, styrene and trichloroethane. In each case, chemical evaporated from the water solution. However, the contribution of the evaporated chemical to the vapor space concentration was minimal. All three tanks gas freed essentially as though the chemical/water residue was not present. The net result was that predicted concentrations during tank entry were below the respective TLVs of the chemicals. In the case of ethyl benzene, the liquid phase resistance controlled the evaporative mass transfer. For trichloroethylene and styrene the liquid and gas phase resistances to evaporation were of comparable magnitude.

Class III. This response class included methyl isobutyl carbinol, methyl acetate and ethanolamine. The distinctive feature of this group was that the liquid phase (aqueous solution) offerred little resistance to solute evaporation. The net effect of the solute evaporation was that the gas freeing process was retarded to the extent that vapor concentrations at the time of tank entry equalled or exceeded the respective TLVs.

Tier I Evaluations. The pertinent data for Tier I toxicological evaluations of the predicted exposures to a crewman as a result of entry into a tank containing each of eight residual chemicals are summarized in Table V-8. In this table, the predicted concentration range and average exposure

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TABLE V-8. PREDICTED EXPOSURES TO SELECTED CHEMICALS DURING TANK ENTRY

Sequence No.	Chemical	Chemical Abbreviation	Exposure Concentration Range, (ppm)*	Average Exposure Concentration (ppm)	TLV-TWA (ppm)	TLV-STEL (ppm)	TLV-C (ppm)	Toxicological Significance/** Comments
1	1,2,4-Trichlorobenzene	TCB	320	320	5	--	--	MMRL
2	n-Hexane	HXA	21,000-4800	11,000	50	--	--	MMRL
3	Ethyl benzene	ETB	24-5.4	12	100	125	--	NTS
4	Styrene	STY	10-2.3	5.2	50	100	--	NTS
5	1,1,1-Trichloroethane (methyl chloroform)	TCE	180-43	95	350	450	--	NTS
6	Methyl isobutyl carbinol (skin)	MIC	110-92	100	25	40	--	MMRL
7	Methyl acetate	MIT	4000-2800	3400	200	250	--	MMRL
8	Ethanolamine	MEA	6.2-6.0	6.0	3	6	--	MMRL

* The larger value indicates vapor concentration in the tank at the time of entry. The lower value is the vapor concentration at the conclusion of work and egress from the tank. When the concentration declines, vapor is removed by ventilation faster than it is generated by evaporation from the liquid. Where there is no variation in concentration over the work period, the chemical evaporation rate is constant and equal to the rate of vapor removal by ventilation.

** MMRL = Exposure meets criterion of medical monitoring response level.

NTS = Not of toxicological significance because exposure concentration is below medical monitoring response level.

concentration of each chemical are given for the 30-minute exposure during the in-tank activities. Each tank entry is considered as a separate exposure for toxicological assessment; the sequences are not combined as sequential entries for evaluation. If entries into tanks containing different chemicals were made sequentially by the same crewman, potentiating interactions between chemicals could occur, depending on the particular chemicals, the exposure concentrations and the durations of time between entries.

In three of the eight tank entry sequences, (Sequence Nos. 3, 4, and 5), predicted average concentrations of the chemicals, ethyl benzene (ETB), styrene (STY), and 1,1,1-trichloroethane (TCE) do not equal or exceed 50 percent of the TLV-TWA values for these chemicals and do not meet the criterion of a medical monitoring response level. Concentration excursions of these chemicals, as indicated by the predicted exposure concentration ranges during the 30-minute exposure period, also are below these exposure limit values. Therefore, these exposures are not considered toxicologically signif-icant and are not further discussed. In the other five sequences (Sequence Nos. 1, 2, 6, 7 and 8), the predicted average concentrations of chemicals exceed at least 50 percent of the TLV-TWA values and meet the criterion of a medical monitoring response level. An indepth toxicological assessment of these exposures is presented in the Tier II evaluations.

Tier II Evaluations. In Sequence No. 1, the predicted average concentration of 1,2,4-trichlorobenzene (TCB) during the 30-minute tank entry is 320 ppm. This concentration considerably exceeds the TLV-TWA value (5 ppm) which is also a ceiling limit value. TCB is an irritant and also produces systemic effects in a variety of target organs. In a study by Treon (10) of the acute and subacute inhalation toxicity of TCB, non-lethal exposures of animals were found to cause damage to the liver, kidney and ganglion cells of all levels of the brain. Brown et al. (10) reported that acute exposures at 70 to 200 ppm did not kill rodents or cause organ pathology but did produce lethargy and retarded weight gain. Human exposure data are very limited and are insufficient to enable prediction of toxic effects or symptoms that may result from a 30-minute exposure to 320 ppm. In a study of industrial human exposures, it was reported that minimal eye and throat irritation occurred at 3 to 5 ppm in some workers (10). From these data, it would appear that, at

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least eye and upper respiratory tract irritation would be experienced by a crewman exposed to the concentration of TCB predicted during tank entry and that more severe effects would be possible.

In Sequence No. 2, the predicted average concentration and the concentration range of n-hexane (HXA) in the tank considerably exceed the TLV-TWA value of 50 ppm and excursions permitted by this limit value. These concentrations also exceed the NIOSH IDLH value of 5000 ppm for HXA. The toxicity of HXA was reviewed in Section IV.3.1. The most pertinent data are those reported by Drinker and others (10) and by Patty and Yant (10). The former investigators found that human exposures to 1400 to 1500 ppm produced slight nausea, headache and eye and throat irritation. The latter investigators reported that an exposure of man to 5000 ppm for 10 minutes caused marked vertigo. Therefore, at the predicted average concentration of 11,000 ppm of HXA in the tank, which is more than two times the IDLH value, marked central nervous system depressant effects would be anticipated. This exposure could result in serious consequences to the worker and constitutes a definite hazard. Exposure to the maximum concentration (21,000 ppm), which is more than fourfold the IDLH value, of the predicted exposure concentration range would produce even more severe depressant effects and, possibly, narcosis.

In Sequence No. 6, the predicted average concentration of 100 ppm of methyl isobutyl carbinol (MIC) exceeds the TLV-TWA (25 ppm) and the TLV-STEL (40 ppm) values for this chemical. The toxicity of MIC has not been well established. In one of the few animal studies of this chemical, Carpenter and Weil (10) reported that a two-hour exposure of rats to the saturated vapor resulted in no deaths but that five of six rats died after an eight-hour exposure to 2000 ppm. In a human study by Silverman and others (10) of sensory response to MIC, eye irritation was produced by a concentration of 50 ppm. The TLV-STEL of 40 ppm was recommended by the ACGIH to prevent eye irritation and to provide a safety factor for possible systemic effects of MIC. At the average concentration of 100 ppm predicted for tank entry, at least irritation of the eyes would be expected to occur. More serious effects could result from dermal absorption of MIC, particularly if a significant area of the skin were exposed to the chemical. This chemical has

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an ACGIH "Skin" notation, indicating that sufficient quantities may be absorbed through the skin to invalidate Threshold Limit Values.

The predicted average concentration of 3400 ppm of methyl acetate (MTT) during tank entry in Sequence No. 7 considerably exceeds the TLV-TWA (200 ppm) and TLV-STEL (250 ppm) values and permissible excursion limits. The concentration also exceeds the IDLH value of 1000 ppm. The toxicity of MTT was reviewed in Section V.3.2. Although data relevant to human acute exposures are limited, it has been reported that MTT is an irritant and also causes ocular and nervous disturbances in workers exposed to the vapors (10). Inflammation of the mucous membranes of the eyes and respiratory passages, nervous irritation and tightness of the chest are among the symptoms observed. Henderson and Haggard (10) suggested that methanol formed by hydrolysis in the body might be responsible for the toxicity of MTT. The high concentrations predicted for tank entry are likely to produce marked irritation and inflammation of the eyes and respiratory passages and severe ocular and nervous system effects. If MTT is, indeed, metabolized to methanol in the body, the predicted exposure may even be sufficient to cause damage to the optic nerve.

In the last sequence, Sequence No. 8, the predicted average concentration of 6.0 ppm of ethanolamine (MEA) during tank entry exceeds the TLV-TWA (3 ppm) for this chemical and is equal to the TLV-STEL concentration. However, a TLV-STEL value limits an exposure to 15 minutes at the time-weighted average concentration; therefore, the 30-minute exposure during tank entry exceeds this limit value. Ethanolamine has irritant and necrotic effects on the skin and also may produce systemic effects. In several rodent species exposed to MEA, Treon et al. (14) reported that observed effects were primarily those of respiratory tract irritation. Pathological changes in animals exposed to higher concentrations were chiefly those of pulmonary irritation with some nonspecific degenerative changes in the liver and kidneys. In a study by Weeks (14), dogs, rats and guinea pigs survived 90-day exposures to concentrations of from 12 to 25 ppm. In spite of the wide use of this chemical in industry, there are no reports of injury to workers (10). Because of limited human exposure data, ACGIH TLVs have been based primarily on the results of animal exposure studies. The TLV-TWA of 3 ppm and the TLV-

STEL of 6 ppm were recommended by the ACGIH to avoid possible irritant and systemic effects of the chemical. Although the predicted exposure to MEA during tank entry exceeds these limit values, toxic effects other than, possibly mild eye, skin and respiratory tract irritation are not anticipated.

V.3.4 Dermal Exposures

This section presents a hypothetical scenario that involves a dermal exposure to a bulk liquid cargo. While the scenario is hypothetical, its elements appear to be realistic based on an accumulation of observations. The scenario, then, should be plausible.

This hypothetical scenario involves the transfer of commercial grade carbon tetrachloride from a barge to a parcel chemical tanker. All three of the barge's 140,000 gallon tanks (10,000 bbl total) were filled with product when the barge came alongside the ship. The plan was to transfer 126,000 gallons of carbon tetrachloride from one of the barge tanks to the 4CA tank on the ship. At 126,000 gallons, 4CA would then be 98 percent full. After transfer to the ship had been completed, the remainder of the product was then scheduled to be delivered to another client. The discharge pump on the barge was rated at 105,000 gpn; thus, actual transfer time was projected to be about 1.2 hours. Because of the short discharge time, the towboat was to remain connected to the barge.

After the barge was secured, hose hookup commenced. As the ship was lightly drafted, the barge did not have sufficient length of hose to reach the ship's manifold. The ship provided an adequate length of infrequently used hose that had been stored in the forepeak. The hose hookup was completed first at the ship's manifold by the ship's crew. The ship's crane was then used to lower the free end of the hose to the barge deck. The barge tankerman proceeded to secure the hose flange to the barge manifold flange using two bolts (USCG Regulations in 29CFR Part 35 require a minimum of three bolts). A somewhat worn jacketed gasket was placed between the flanges.

The barge discharge pump was started, and flow was established from the barge center tank into the ship's cargo tank. As the ship had no

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extra walkie talkies, the barge and the ship communicated primarily by hand signals. Voice communication was not totally possible because of the noise generated by the diesel drive on the pump. The ship's cargo transfer officer signaled by hand that everything was proceeding correctly. The barge tanker-man then retired to the towboat for a snack. As it was his usual practice during break, he drank a couple of beers. Between these breaks and shore-side socializing with co-workers, the tankerman normally consumed an average of a 6-pack per day. Alcohol consumption has been observed aboard tankers. While consumption has not been observed in barge operations, it is reasonable to assume that it does.

The transfer operation took place on a fall evening. For warmth, the tankerman wore work pants and a flannel shirt under a pair of coveralls. Cloth gloves were worn while on deck.

Over the course of the transfer, the tankerman gauged the tanks by draft several times but not with an ullage tape.

At 70 minutes into the transfer, the tankerman reappeared on deck. The Mate on the ship deck above him was gesturing and shouting to shut down the transfer pump. Gauging of the ship's tank with a tape had indicated that the final ullage had been reached, and continued loading would create the possibility of a deck spill. The tankerman checked the barge draft and indi-cated that the final draft corresponding to the scheduled transfer quantity had not yet been reached. The source of the disagreement was that the tanker-man was basing his decisions on a printed table that related transferred product volume to draft difference for various cargo specific gravities. He had made an error in reading the table and had incorrectly concluded that the final draft or draft difference had not yet been reached and more cargo needed to be pumped.

By this time, the situation was crucial on the ship. To avoid a spill, the cargo transfer officer ordered a crew member to shut down the ship's manifold valve against the oncoming flow even though it is not an accepted procedure. When the cargo transfer hose burst at the barge manifold, the tankerman was standing next to it. Before he could react, the tankerman's

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entire front side was drenched with carbon tetrachloride. The chemical penetrated the coveralls, flannel shirt and work pants. As quickly as possible, he shut off the barge's diesel driven discharge pump. In addition to the product that was already on deck, carbon tetrachloride also drained by gravity from the burst hose because the barge was below the ship. The product was retained on deck by the spill rails that had recently been installed.

The tankerman proceeded to disconnect the hose, secure the flange at the barge manifold, spread a solid sorbent on the deck, and make ready to sail. During these activities, accumulated product on the deck penetrated his leather boots to the skin.

Dermal contact with carbon tetrachloride existed for approximately the one hour between when the hose burst and when the barge separated from the ship. He was then able to remove his clothes and take a shower.

Tier I Evaluation. In this hypothetical scenario, a tankerman was exposed to carbon tetrachloride (CBT) when the cargo transfer hose burst at the barge during transfer of CBT from the barge to a parcel chemical tanker. The CBT drenched the tankerman's clothing and penetrated his leather boots. He did not remove his clothing and shower for approximately one hour after the accident occurred. During this time, the tankerman was exposed both by inhalation of CBT vapors and by cutaneous absorption of liquid CBT from the clothing and boots. Inhalation exposure occurred as a result of volatilization of CBT liquid during the spill and from the drenched clothing. Although it is not possible to determine the concentrations of CBT vapor to which the tankerman was exposed during the approximately one hour exposure, the concentrations, particularly during and for a time after the spill, most likely exceed at least 50 percent of the TLV-TWA value (5 ppm) for this chemical and meet the criterion of a medical monitoring response level. Even if the concentrations were below this value, the threshold limit is invalidated by the potential for extensive cutaneous absorption of liquid CBT in this scenario. The ACGIH has identified CBT with a "Skin" notation to refer to the potential contribution to the overall exposure by the cutaneous route. The ACGIH states that "this attention-calling designation is intended to suggest appropriate measures for the prevention of cutaneous absorption so that the threshold

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limit is not invalidated" (15). Thus, the exposure in this scenario meets the criterion of a medical monitoring response level and an in-depth toxicological assessment of the exposure is presented in the Tier II evaluation.

Tier II Evaluation. The toxicity of carbon tetrachloride (CBT) was reviewed previously in Section IV.3.3. However, because of the potential for and probability of cutaneous absorption of large quantities of CBT in this hypothetical exposure, the toxicity from dermal exposure to this chemical is emphasized in this evaluation. Absorption of liquid CBT through the skin of animals and humans has been demonstrated experimentally. In a study with rabbits, Lapidus (16) found CBT in the blood, liver and fat of four animals after immersion of one ear of each rabbit for 5, 6, 8 or 9 hours. In a study with human volunteers, Stewart and Dodd (17) measured CBT in the alveolar breath of subjects who each immersed one thumb in liquid CBT for 30 minutes in a manner than prevented inhalation of CBT vapors. The magnitude and significance of the controlled dermal exposure was estimated by comparing the concentration of the chemical in the alveolar air with previously obtained data of the alveolar breath concentration following a vapor exposure to a known concentration of CBT. The investigators concluded that the amount of CBT that can penetrate the skin depends on 1) the type of skin exposed, with thickness, vascularity, age and chemical composition being factors; 2) the area of skin exposed; and 3) the duration of the skin exposure. With total immersion of one thumb for 30 minutes, the peak alveolar concentration of CBT was slightly less than 1 ppm during the exposure and measurable amounts of CBT were present in exhaled air 5 hours post exposure. Using these data, the investigators estimated that immersion of both hands for 30 minutes, which would increase the skin area of one thumb approximately fortyfold, would be approximately equivalent to a 30-minute vapor exposure to 100 to 500 ppm. These investigators estimated that both hands comprise 4 percent of the total body surface area and the area below the umbilicus comprises 50 percent of the total area. In this hypothetical scenario, it is likely that at least 30 percent of the tankerman's body surface area had contact with CBT during a one-hour period. This cutaneous exposure would be equivalent to a 60-minute vapor exposure of at least from 750 to 3750 ppm. These concentrations considerably exceed the IDLH value of 300 ppm for CBT.

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There have been numerous cases of poisonings by CBT because of its widespread use for many years in a variety of industries. Most of these cases resulted from chronic exposure although there are several reports of acute poisonings. Dermal absorption could have been a major contributing factor in many of these cases, but it was not considered by the investigators (18). Of those cases of acute poisoning by inhalation, the concentrations of CBT vapor were measured or reported in only a few. In one report, three workers acutely exposed to CBT were hospitalized with jaundice, nausea and dizziness (19). The highest concentration to which one of the workers was exposed was reported as from 75 to 600 ppm with the "main" level at 210 ppm. Experimental human studies of nervous system responses to inhaled CBT were conducted by Lehmann and Schmidt-Kehl (20). Volunteers were exposed to concentrations that ranged from 140 ppm to 14,000 ppm and for periods ranging from 50 seconds to 30 minutes. The investigators reported that the only effect of exposure at 240 ppm for 20 minutes was perception of a light, transient odor but that dizziness and vertigo occurred after 10 minutes of exposure to 600 ppm. Exposure to concentrations higher than 600 ppm resulted in increasingly severe effects that included headache, tiredness, giddiness and salivation. Loss of consciousness occurred with exposure to 14,000 ppm for 50 seconds. In a similar experiment, Davis (21) reported no effects after 5 hours exposure to 75 ppm, slight nausea after 30 minutes exposure to 160 ppm, and nausea, vomiting and headache after 30 minutes of exposure to 320 ppm. Based on these literature reports, the quantity of CBT absorbed cutaneously from the tankerman's clothing could produce symptoms of dizziness, vertigo and even unconsciousness and could result in severe damage to the liver, kidneys and central nervous system.

The dermal exposure of the tankerman could be even more hazardous because of his prior intake of alcoholic beverages. It has been well established from epidemiologic evidence and animal studies that the toxicity of carbon tetrachloride and the risk from exposure may be increased by the use of alcohol (18). In patients hospitalized following CBT exposure, Abbott and Miller (22) considered alcohol to be a predisposing factor in 8 of 10 cases; Joron et al. (23) reported alcohol involved in 8 of 12 cases; and New et al. (24) found alcohol was involved in 17 of 19 cases. In the report by New et al. (24), the serious cases of renal failure all involved alcohol consumption.

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V.4 Summary

In this section of the document, hypothetical exposure data involving four types of operational activities were presented and toxicological evaluations were made of these data. Although the data are hypothetical, the data for the first three categories of operations (open gauging, deck work downwind of tank loading and tank entry) are realistic predictions based on certain assumed operating conditions, the physical properties of the applicable chemicals and analytical computer models of tank ventilation and plume dispersion. For the fourth operation which involved the transfer of chemical from a barge to a tanker, an accidental situation involving the spillage of a chemical with potential for dermal absorption was assumed.

From the toxicological assessments of the hypothetical data, it is apparent that many of the work sequences would result in hazardous exposures of crewmen. Under certain assumed (but realistic) conditions, the predicted concentrations of certain chemicals considerably exceed Threshold Limit Values. In some sequences, the levels are sufficiently high to cause serious toxic effects, and even death, in exposed crew members. These assessments of hypothetical data emphasize the need for the use of proper protective equipment and clothing by marine personnel as well as for a maritime medical and environmental monitoring program.

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VI. CONCLUSIONS

Industrial exposure guidelines based on a conventional 8-hour work day, 40-hour work week, are not directly applicable to chemical exposures encountered during marine operations. Present limit value adjustment models also have limitations in their application to marine operations. Therefore, it was necessary to develop a practical method, based on industrial exposure limit values, to evaluate the toxicological hazards of exposure to chemicals by marine workers. The evaluation method incorporates the concept of a medical monitoring response level which was defined to be equal to one-half of the applicable TLV-TWA. Exposures less than the medical monitoring response level are judged to be acceptable. Exposures that equal or exceed the medical monitoring response level are considered to be toxicologically significant for medical monitoring purposes, independent of exposure duration. Those exposures which meet the criterion of a medical monitoring response level are further evaluated to determine the nature and severity of toxic effects which may be anticipated.

For these evaluations, marine work activities were monitored and characterized in detail, and several hundred exposure samples were collected. From these, a subset of more than 200 exposures was selected for evaluation; these samples represent a wide range of activities, including tank loading and off-loading, tank gauging, tank entry and cleaning, and various on-deck activities. In addition, 1) measured exposures were combined into hypothetical exposure sequences and 2) hypothetical, but realistic, exposures were predicted for additional chemicals and selected work activities in order to provide a more comprehensive evaluation of the marine environment. Toxicological assessments were made of the measured and hypothetical exposure data and the following conclusions were reached:

1) The two-tiered approach that was developed is a conservative and practical method for toxicological evaluation of exposures of marine workers to chemicals. The Tier I evaluation readily differentiates between exposures that are not of toxicological significance and do not require further consideration and those exposures that are of significance. The Tier II evaluation provides an assessment of the potential toxicity and hazard of those exposures that are toxicologically significant.

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2) It is apparent from the evaluations of both the measured and the predicted exposure data that the marine environment is a toxicologically hostile environment. In some work activities, concentrations of chemicals may be sufficiently high to cause marked toxic effects, and even deaths, in exposed marine workers.

3) Host factors and environmental/work conditions unique to marine operations may potentiate the toxicity of chemicals in the marine environment.

4) In marine operations, the potential exists for exposure of workers to chemicals that are suspect human carcinogens. In certain work activities, concentrations of these chemicals may considerably exceed the medical monitoring response level.

5) During certain work activities, particularly tank entry and open tank gauging, there is a greater potential for exposure to hazardous concentrations of chemical vapors.

6) In contrast to industrial exposures for which considerable epidemiological, accidental exposure, and experimental exposure data exist for many chemicals, there are insufficient data to predict the effects of marine environmental/work conditions and host factors on the toxicity of chemicals.

7) There are insufficient epidemiological data relevant to the development of cancer among marine workers to estimate the hazards of repetitive, sequential and simultaneous exposures to carcinogenic chemicals in marine operations.

8) Because the marine environment is a toxicologically hostile and hazardous environment, the need exists to control and reduce exposures of marine workers to chemicals and to monitor their health status.

VII. RECOMMENDATIONS

The results of the assessment of occupational exposures to chemical vapors have clearly demonstrated that the marine work environment is a toxicologically hostile environment.

1) During certain work activities, measured concentrations of some chemicals frequently exceed Threshold Limit Values, and

2) Toxicologically significant exposures were measured for chemical substances which are highly toxic and have the potential of producing severe damage.

Corrective measures are needed to reduce observed toxicological hazards in the marine work environment. This corrective action will require implementation of a marine occupational safety and health program which includes an effective industrial hygiene program to control, reduce, and monitor exposure levels, and an adequate medical monitoring program to serve as a safety net. Once these measures are in place, continuing toxicological assessment, using the procedures outlined in this report, will be needed to evaluate the effectiveness of the corrective measures implemented and to recommend modifications, if needed.

The occupational safety and health program recommended to reduce toxicological hazards in the marine work environment includes the following elements:

1) Development and implementation of appropriate engineering controls to reduce workplace concentrations;

2) Development and use of safe work practices;

3) Determination and provision of appropriate protective gear;

4) Provision of adequate training and education regarding handling of toxic chemicals;

5) Routine monitoring of environmental concentrations in confined spaces before entry;

6) Establishment of routine industrial hygiene survey audits of standard work practices;

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7) Consideration of biological monitoring methods for appropriate chemical substances and work activities; and

8) Establishment of medical monitoring, at specified intervals, of all personnel potentially exposed to toxic chemicals in their routine duties.

Specific recommendations for certain elements of the marine safety and health program are presented as follows:

1) Open gauging is currently permitted for all Subchapter D cargos and certain Subchapter O cargos. It has been demonstrated through actual measurements and justifiable predictions that open gauging at or near tank top-off may result in toxicologically significant exposure levels. Therefore, it is recommended that the basis for the open gauging minimum requirements in Subchapter D be thoroughly reviewed to identify cargos for which the requirements should be upgraded to at least restricted gauging systems. This review process should include:

   ° application of the Criteria for Hazard Evaluation of Bulk Chemicals which is contained in the IMO Chemical Code;

   ° screening criteria and exposure prediction methods such as those that have been applied in this report; and

   ° toxicological interpretation methods similar to those in this report.

   Prior to the USCG adoption of the IMO Chemical Code, cargos that presented flammability hazards rather than toxicity hazards were classified as Subchapter D products. Accordingly, open gauging was permitted for these products. In recent years, knowledge of the toxicity of industrial chemicals has expanded greatly. The result has been (1) establishment of TLVs where none may have existed and (2) a reduction of previously established TLVs. As an example, n-Hexane is a Subchapter D chemical whose TLV was reduced by the ACGIH during the course of this project. Therefore, it is likely that the recommended review, which would incorporate the IMO chemical code, would identify Subchapter D chemicals whose toxicity properties now outweigh flammability considerations. These chemicals would be candidates for reclassification into Subchapter O with a minimum requirement of restricted or closed gauging as appropriate. This review would permit a reassessment of the open gauging minimums that were specified prior to USCG adoption of the IMO Chemical Code.

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2) Minimum vent height requirements are currently specified for
    Subchapter O chemicals. It is recommended that the USCG apply
    the ON-DECK (Reference 1 of Chapter IV) plume dispersion model
    to reassess the vent height requirements for Subchapter O
    chemicals and to specify vent height minimums for Subchapter D
    chemicals. The objective of this effort would be to identify
    vent height minimums under worst case loading conditions which
    would minimize toxicologically significant exposures on deck,
    downwind of a tank that is being loaded. This recommendation
    presumes that the selected venting method would be used
    during cargo loading, not just during transit.

3) Tank entry has the potential for toxicologically significant
    exposures to chemical vapors. Subchapter O, Part 153 is quite
    clear on the preentry requirements for toxic vapor measure-
    ments at the TLV level and the conditions under which self-
    contained breathing apparatus (SCBA) is required. There does
    not appear to be a similar tank entry requirement in Sub-
    chapter D. Therefore, it is recommended that the USCG study
    the feasibility of including in Subchapter D a section on tank
    entry that is analogous to that of Subchapter O. It is also
    recommended that the USCG incorporate by regulatory reference,
    the appropriate chemical-specific TLV concentrations that are
    implied in Part 153.

4) An important part of these recommendations is the implementa-
    tion of a hazard communication system and work practice train-
    ing, which would include the use of protective equipment,
    respirators and oxygen, combustible gas and toxicity testing
    instruments. The recommended hazard communication system
    could be modeled after OSHA's Hazard Communication Standard
    (29CFR 1910.1200) which incorporates a formal written communi-
    cation program, Material Safety Data Sheets, labeling, em-
    ployee information and training. The intent of this Standard
    is to evaluate and communicate chemical hazards to employees.

5) Establishment of safe work practices which are chemical and
    work scenario specific is recommended. The safe work prac-
    tices should include monitoring of toxic concentrations in
    confined spaces before entry and at regular intervals during
    extended periods of work activities in these spaces. Employ-
    ment and use of a confined space entry permit to monitor and
    regulate all confined space entry activities are also recom-
    mended.

6) Implementation of a regularly scheduled industrial hygiene
    survey audit to monitor established safe work practices is
    recommended. The industrial hygiene survey should include
    observation and evaluation of standard work practices and
    procedures, and personal dosimetry to confirm that routine
    exposures are below toxic threshold limits.

7) The use of non-invasive biological monitoring methods which require minimal training of both worker and medical staff and which offer no inherent risk to the individual worker is recommended for consideration in marine operations. Invasive biological sampling methods such as venipuncture are not recommended because of the extensive requirements for cleanliness and training, and because of inherent risk to the worker. Potential use of biological monitoring methods is restricted to chemical substances for which sufficient toxicological and epidemiological data are available to support practical interpretation of the results. Biological monitoring of occupational exposures should be considered for the following circumstances:

   ° In response to known or suspected acute overexposure to a specific mixture or single substance;

   ° To determine whether or not protective gear worn in extremely hazardous environments adequately protects the worker from absorption of excessive internal doses through respiratory or dermal routes;

   ° To augment routine industrial hygiene environmental measurements for marine operations involving extremely toxic substances (such as carcinogens) in potentially hazardous work scenarios.

   In the future, as biological monitoring techniques are developed for more chemicals, this type of non-invasive monitoring may play a more significant role.

8) All personnel who are potentially exposed to toxic chemical substances in their routine duties should be medically monitored to detect early signs of occupational disease. Medical examinations should be provided at regular intervals and should emphasize target organs and laboratory tests which relate to toxic chemical exposures. In addition to standard work history and medical history information, the results of environmental monitoring and biological monitoring should be made available to the examining physician to aid evaluation of health effects potentially resulting from toxic chemical exposures.

9) Since a "safe" level of exposure to any of the carcinogenic chemicals may not be assumed, the following recommendations are made to reduce the probability of development of cancer from these exposures:

   ° Marine workers should be made aware of the identity of carcinogenic chemicals and of the fact that the effect of these chemicals may not occur

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until many years after exposure. Extreme precautions should be taken by marine workers to avoid exposure to chemicals designated carcinogens as well as to other highly toxic chemicals.

o A specially tailored industrial hygiene program to vigorously control exposures to all carcinogenic chemicals should be implemented. The aim of this program should be to reduce exposure levels of the lowest possible level and certainly to below Threshold Limit Values.

o All exposures of personnel to carcinogenic substances should be recorded because it is unlikely that any program will completely eliminate all exposures to carcinogenic substances. This information should be used 1) to establish the data base for an epidemiological study for public health use, 2) to enable possible restriction of marine workers from ships trans porting carcinogenic chemicals when these workers have reached a certain exposure level, as established by occupational medical personnel, and 3) to correlate with medical monitoring findings.

APPENDIX A

LIMIT VALUE ADJUSTMENT MODELS

Currently, there are five models or methods for adjusting TLVs in unusual work schedules.

- o   Hickey-Reist (Reference A-1)
- o   Roach (Reference A-2)
- o   Mason-Dershin (Reference A-3)
- o   Brief-Scala (Reference A-4)
- o   OSHA Field Manual (Reference A-5)

All of these models, which are discussed below, have been published within the past 10 years.

Hickey-Reist Model

The Hickey-Reist model for adjustment of vapor inhalation TLVs assumes that the body is a well mixed, one-compartment reactor. Conservation of mass equations are used to describe the accumulation of contaminant burden within the body during periods of exposure as well as the reduction of body burden during non-exposure periods. Exposure levels are assumed to be at the same constant level for all work periods. Contaminant uptake and excretion by respiration are assumed to be first order, constant rate processes. The governing equations are applied in a piecewise fashion to formulate peak body burden expressions for the conventional work schedule and a completely general novel work schedule. Equating of peak body burdens, which implies equal protection of the worker in the novel schedule, results in a general expression for the TLV adjustment factor, F_p. For a given substance and work schedule, the calculated value of the adjustment factor is multiplied by the existing TLV or PEL to arrive at an exposure limit for the novel schedule. When the work cycle and the distribution of work shifts within the cycle are repetitive, the expression for F_p is as follows:

$$F_p = \frac{(1-e^{-kt_{1n}})\,(1-e^{-nk\,(t_{1n} + t_{2n})})\,(1-e^{-kT_s})\,(1-e^{-k\,(t_{1s} + t_{2s})})}{(1-e^{-kt_{1s}})\,(1-e^{-mk\,(t_{1s} + t_{2s})})\,(1-e^{-kT_n})\,(1-e^{-k\,(t_{1s} + t_{2s})})} \qquad (1)$$

where t_{1n} = normal 8-hour work day

t_{2n} = normal 16-hour biological purge period

T_n = normal 168-hour week

n = 5 days in a normal work week

t_{1s} = work shift length in a novel schedule

t_{2s} = biological purge period between consecutive shifts in the novel schedule

T_s = length of the periodic work cycle

m = number of equivalent work days in the novel work week

k = composite uptake/excretion rate by respiration $(hr)^{-1}$.

The rate constant, k, is related to the biological half-life of a chemical substance, $T_{1/2}$, through the following relationship:

$$k = \ln2/T_{1/2} \tag{2}$$

If the substance in question is also metabolized, then the constant k is replaced by $k_1 + k_2$ where k_1 is the rate constant for respiration, and k_2 is the rate constant for metabolism or destruction of the parent chemical.

From an operations standpoint, the difficulty in applying the Hickey-Reist model to maritime work schedules is that the exposure environment is not constant from shift to shift throughout the work cycle. Previous discussions have indicated the exposure level is highly variable throughout a voyage, and there may be extended periods of minimal or no exposure. Assuming, however, that such a condition were to exist, then the following example illustrates the form of the adjustment factor, F_p.

Assume a work cycle that consists of alternating periods of 30 days on and 30 days off. For the traditional maritime schedule, there are two novel, 4-hour work shifts each 24-hour day. Each shift is separated by an 8-hour rest period. Under these conditions, the parameters in the Hickey-Reist model have the following values:

$$t_{1s} = 4 \text{ hours}$$
$$t_{2s} = 8 \text{ hours}$$
$$T_s = 1440 \text{ hours (hour equivalent of 60 days)}$$
$$m = 60 \text{ (2 work shifts on each of 30 days)}$$

The adjustment factor equation then takes the following form.

$$F_p = \frac{(1-e^{-8k})\ (1-e^{-120k})\ (1-e^{-1440k})\ (1-e^{-12k})}{(1-e^{-4k})\ (1-e^{-120k})\ (1-e^{-168k})\ (1-e^{-24k})} \tag{3}$$

A numerical evaluation of the above equation for a range of biological half-lives is summarized below.

$T_{1/2}$ (hrs)	F_p
1	1.06
5	1.32
10	1.22
50	0.95
100	0.85
500	1.02
1000	1.17
5000	1.36
10000	1.40

The F_p profile for this maritime schedule demonstrates some interesting features:

o   For very long half-life substances, the TLV would be increased. The percentage increase, relative to current standards, asymptotically approaches a level that is proportional to the total hours of exposure irrespective of the detailed work schedule.

o   The TLVs for substances with half-lives greater than about 20 but less than 500 hours may be decreased in order to satisfy the peak body burden (equal protection) criterion. The above two observations are qualitatively similar to those predicted by Hickey and Reist for shift work involving three 12-hour days per week.

o   For substances with half-lives less than roughly 20 hours, the TLVs may be increased. This observation differs from the F_p predictions of Hickey and Reist for

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any land-based, unusual shiftwork schedule. Alternatively, maintenance of existing TLVs for substances with half-lives in this range would result in peak body burdens for this maritime schedule that are lower than the corresponding burdens in the conventional work shift/exposure scenario.

Hickey and Reist address the issue of adjusted excursion limits above the TLV-TWA but within the context of an 8-hour work day. Similar predictions can be made for the maritime work schedule in the previous example. As opposed to 4-hour continuous exposures on each watch, assume that the exposure duration, t, is less than four hours on each watch and that there is no exposure for the remainder of the 4-hour watch as well as during the 8-hour rest period. On this basis, an expression analogous to Equation 3 could be derived. The only difference between the expressions would be the first term in the denominator of Equation 3. For illustrative purposes it is easier to use Equation 4.

$$F_{pst} = F_p \frac{(1-e^{-4k})}{(1-e^{-kt})} \qquad (4)$$

where F_{pst} = adjustment factor for excursions above the TLV-TWA;

F_p = adjustment factor as predicted for maritime work/ exposure schedule using Equation 3; and

t   = exposure duration each shift (less than four hours).

F_p for a substance with a 5-hour half-life is 1.32, and the rate constant, k, is 0.1386. Applying these values to Equation 4 for various exposure times results in the following values for F_{pst}.

t (hrs)	F_{pst}
0.5	8.39
1.0	4.34
2.0	2.32

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Thus, under the equal protection criterion, one half-hour exposure could be tolerated each day at a level of roughly eight times the TLV-TWA. Note that 15-minute exposures are not considered because the model does not accurately describe the pharmacokinetics of short-term exposures. The above procedure could be used to generate a family of curves of F_{pst} versus $T_{1/2}$ with excursion time as the parameter.

The above numerical values were derived from a model that is based on equal body burden protection. These predictions are not meant to take precedence over established exposure guidelines because the model requires validation.

Roach Model

As in the Hickey-Reist model, the Roach model also incorporates first order uptake and respiratory elimination, constant exposure level and the concept of equality of peak body burden. The model accepts constant workshift lengths but rest (no exposure) periods of arbitrary duration. The model for TLV adjustment is based on an expression that represents the ratio, R, of peak body burden in the conventional schedule to the body burden at the end of any given shift in the novel work schedule.

$$R = \frac{(1-e^{-8a})\,(1-e^{-120a})\,(1-e^{-1a})}{(1-e^{124a})\,(1-e^{-168a})\,(1-e^{-ma})\,\left(\sum\limits_{i=1}^{j} e^{-n_i a}\right)} \tag{5}$$

where a = uptake/excretion rate

l = total hours in a complete novel work cycle

m = duration of the novel work shift

For clarity, the summation in the denominator can be expanded

$$\sum_{i=1}^{j} e^{-n_i a} = e^{-n_1 a} + \ldots + e^{-n_i a} + \ldots + e^{-n_j a}$$

where n_i = number of hours from the end of shift j to the end of the i-th shift in the cycle.

By definition, n_j is equal to zero. The key to the application of Equation 5 is to identify the shift in the novel work cycle that corresponds to the peak body burden for the entire schedule. This involves calculation of Σn_i for each shift in the cycle. The shift end that produces the minimum value of Σn_i corresponds to the shift that results in the peak body burden. The minimum value of the summation also corresponds to the minimum value of R which satisfies the equal peak body burden criterion. The procedure is straight forward, but it can be cumbersome if the rest periods within the cycle are highly variable in duration.

If the novel work schedule involves regular, repetitive work/rest periods as in the traditional maritime work schedule, then the peak body burden occurs at the end of the last 4-hour watch before the vacation period begins. Under these conditions, Σn_i and R are minimum for this last shift, and it can be shown that the adjustment factors for the Roach and Hickey-Reist models are identical. For the example maritime schedule that was used to demonstrate the Hickey-Reist model, the summation in Equation 5 can be expanded and closed to yield:

$$\sum_{i=1}^{j} e^{-n_i a} = \frac{1-e^{(j+1)x}}{1-e^{x}} \qquad (6)$$

where x = -12a and

   j = 59 (the number of 4-hour watches between the end of the last watch and the end of the first watch in the 30-day work schedule)

In the Roach model, l, m and a are equivalent to T_s, t_{ls} and k in the Hickey-Reist model. The adjusted TLV then is the product of R_{min} times the existing TLV-TWA for the 8-hour work day.

Certain substances may have more than one biological half-life. In those cases, Roach recommends that the value of "a" that yields the lowest value of R_{min} be used.

It has been shown that the Hickey-Reist and Roach models are equivalent for the example maritime work schedule. As such, both models predict that the TLV may be increased for substances with short half-lives without violating the peak body burden criterion. However, short half lives are usually associated with substances that have ceiling TLVs or whose TLVs are based on irritation. For those cases, the documentation that forms the basis for the TLV should take precedence over model predictions.

Mason-Dershin Model

The Mason-Dershin model is based on a set of assumptions that are the same as those used in the two previous models. The unsteady differential equation (conservation of mass) for body burden accumulation is integrated for arbitrary work-recovery schedules. This general solution contains a finite series of exponential terms that reflect the overall clearance rate constant. An adjusted TLV-TWA is calculated by equating peak body burden at the end of the last shift in the novel work schedule to the corresponding burden at the end of work on the fifth day of the conventional schedule. The resulting expression is shown below.

$$(\text{TLV-TWA})_N = (\text{TLV-TWA})_5 \, \frac{F_5}{F_N} \qquad (7)$$

where F_5 = fraction of tissue saturation at the close of the work shift in a conventional schedule

F_N = fraction of tissue saturation at the close of the last work shift in the novel schedule

$(\text{TLV-TWA})_5$ = current TWA exposure limit

The ratio, F_5/F_N, is analogous to F_p and R_{min} from the two previous models. Rather than close the finite exponential series in the general solution, Mason and Dershin have tabulated the saturation fraction for various work schedules and durations of exposure. Example tables are presented for methanol and benzene. Using both of these chemicals and two land-based novel work schedules (four 10-hour days and three 12-hour days), TLV adjustment factors were

calculated for both the Mason-Dershin and Hickey-Reist models. The calculated adjustment factors were the same in all cases. The conclusion is that the models are identical. For regular, repetitive novel work schedules, the Hickey-Reist model is more convenient because all exponential series are expressed in closed form. Neither the Hickey-Reist nor the Mason-Dershin models can conveniently account for peak body burdens that occur within a work schedule that consists of a highly variable assembly of work-recovery periods.

The authors of this model state that it is applicable to polar solvents but not solvents that have nonlinear accumulation kinetics (accumulation alters accumulation mechanisms) or to substances that are irritants or sensitizers. The authors do not recommend adjustment of TLV-TWA excursions or TLV-STELs.

Brief-Scala Model

The Brief-Scala model is the first published attempt to cope with exposure limits for non-standard work schedules. The model consists of a TLV-TWA reduction factor and an adjusted excursion factor for exposure above the TLV-TWA. The latter adjustment was derived for use with ACGIH excursion factors that preceded publication of TLV-STELs. Both adjustments account for increased potential for exposure time during the unusual work schedule and the reduced number of hours for biological recovery during off work time. The numerical TLV reduction factor, RF, for the unusual schedule is:

$$RF = \frac{8}{h} \left(\frac{24-h}{16} \right) \tag{8}$$

where   h = hours worked per day

The first term accounts for increased exposure duration or equality of dose; reduced recovery time is reflected in the second term. The above equation can be modified for 7-day work weeks by referencing work-recovery periods to a weekly basis. The excursion factor for the novel schedule takes the following form:

$$EF_N = (EF_{ACGIH} - 1) RF + 1 \qquad (9)$$

The authors indicate that the reduction technique can be used if the TLV-TWA is based on acute or chronic systemic effects and if the ceiling designation is based on chronic toxicity but not irritation. The reduction factor technique is applicable to work periods of reasonable duration. It would not be appropriate for the extended maritime work periods that were described earlier because the model tends toward a zero TLV-TWA as the number of consecutive work hours approaches 24.

OSHA Field Manual

Chapter XIII of the 1979 OSHA Industrial Hygiene Field Operations Manual is entitled "Modification of PELs for Prolonged Exposure Periods." The prolonged periods that are considered essentially represent land-based novel work schedules, e.g. four 10-hour days/week, six 7-hour days/week. As such, the maritime novel work schedule would be excluded. However, there are certain features of the assessment procedure that may have application to the marine work environment.

The adjustment procedure begins with the compound under consideration. Each substance in 29 CFR Part 1910.1000 is assigned to one of six work schedule categories. This categorical assignment governs the extent of allowable PEL adjustment. The six categories and the adjustment criteria are summarized in Table A-I which was extracted from Page XIII-5 of the Field Manual. Examples of products that are shipped by water and which would have no allowable OSHA PEL adjustment are shown below.

An update of the Field Manual based on the 1984-85 ACGIH TLV list would result in marine chemicals such as butanol and gluteraldehyde being included in Category 1A. Categories 2 through 4 permit a PEL adjustment. These adjustments are based on reciprocity, i.e., equivalency of dose between the conventional and novel work schedule. This approach neglects any reduction in the biological recovery period that results from a novel work schedule.

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TABLE A-I. SUMMARY OF WORK SCHEDULE CATEGORIES

Work Schedule Category	Principle Group Characteristic	Conditions Resulting in Adjustment	Adjustment Formula
1A	Ceiling limit standards	None	None
1B	Irritants	None	None
1C	Technologic limitations	None	None
2	Acute toxicity only	Exposed >8 hours/day	Adj PEL= PEL x 8 hours/ hours exposed/day
3	Cumulative toxicity only	Exposed 40 hours/ week	Adj. PEL = PEL x 40 hours/ hours exposed/week
4	Both acute and cumulative toxicity	Exposed >8 hours/day and/or exposed greater than 40 hours/week	The equation for category 2 or 3, whichever results in the greatest protection

Work Category Schedule	Chemicals with no Allowable OSHA PEL Adjustment
1A	Chlorine, Chloroform, Toluene diiosocyanate, o-Dichlorobenzene
1B	Methyl ethyl ketone, Ethyl acetate, Allyl alcohol
1C	Vinyl chloride, Dibutyl phthalate, Benzene

The "no adjustment" criterion for Categories 1A and 1B is clear. Category 1C can be clarified. Substances in this category reflect industries or processes for which there is a physical limit on the state-of-the-art for engineering controls. According to the OSHA categorization, there are few marine chemicals in Category 1C.

The Field Operations Manual was updated in August 1983, but the section dealing with PEL adjustment remained intact. The reference PELs from the 1968 ACGIH TLV list were not updated.

The concept of "no adjustment" of exposure limits for Categories 1A, 1B and 1C may be conveniently applied to the marine environment because the determinations are independent of work schedules. However, if this criterion were to be used, then the reference exposure limits should reflect the most current and conservative values.

On the basis of biological purge period considerations, it is not clear that the adjustments for Categories 2, 3 and 4 are applicable to the marine environment. The adjustments based on reciprocity or equivalency of dose may be applicable for certain substances that are cleared rapidly from the body, e.g., substances with half-lives less than eight hours. However, for substances with half-lives greater than eight hours, the purge period may be insufficient to eliminate residual body burden regardless of the number of work hours preceding the break or the allowable adjusted exposure limit. Adjustments in Categories 2, 3 and 4 should reflect the actual work schedule and the most current exposure limits. Current adjustments do not reflect the decreased purge period.

On the basis of exposure duration, the adjustments in Categories 2, 3 and 4 are not applicable to parcel chemical tankers because the operations that are conducted and the variety of chemicals handled do not result in continuous exposure situations that exceed 8 hours/day or 40 hours/week. Further research would be needed to determine the applicability of Category 2 through 4 adjustments for single product tankers where extended work schedules during tank gauging and cleaning may result in exposure to a single substance for greater than eight hours.

AIHA Unusual Workshifts Committee

In 1983, the American Industrial Hygiene Association established a permanent technical committee to investigate exposure limit adjustments for unusual work shifts and schedules. The problem has been formally acknowledged, and a long-range plan is being formulated. Authors of adjustment factor models are represented on the committee. All available models are being reviewed. This includes single compartment models as well as multicompartment models that can

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describe unsteady pharmacokinetics during variable work/exposure profiles. The long-range goal is to develop chemical specific adjusted TLV tables that are analogous to the ACGIH TLV list for conventional schedules.

Model Predictions and Measured Exposures

Threshold limit value adjustment for the novel marine work schedule and exposure environment is a complex issue. The closed form adjustment factors for the one compartment models all assume a constant shift-to-shift exposure level to a single vapor, which does not occur during tanker operations. In reality, exposure levels within a single voyage are variable, and exposure encounters can be separated by extended periods of the time where there is no exposure to product vapors. This situation is compounded when multiple vapor (mixture) exposures are considered for parcel chemical tanker operations.

In some instances, measured exposures to a single substance vapor have been reasonably constant over nearly two consecutive 4-hour deck watches that were separated by eight hours of no exposure. The exposures resulted from open tank gauging during loading, and no other meaningful exposures were recorded for the next several days. For this situation, it is instructive to calculate and compare the adjusted TLVs assuming that the constant level of exposure were to occur on all deck watches. Due to the equivalency of the one-compartment models, the Hickey-Reist model was used in the following example. The maritime work schedule corresponds to the schedule that resulted in Equation 3. Sample Nos. SB-1 and SB-4, which are presented elsewhere in this report, reflect a nominal 5-ppm exposure to the benzene fraction in gasoline. The actual exposure durations were slightly less than four hours, but for this example 4-hour exposures were assumed. The predictive results are shown in Table A-II. The 1983-84 ACGIH TLV-TWA of 10 ppm for benzene was used to calculate $(TLV\text{-}TWA)_n$, the exposure limit for the novel work schedule. Three biological half-lives were used.

o   A short half-life of 3.3 hours that yields a fast clearance rate as given by Mason and Dershin (A-3).

o   The composite half-life of 7.7 hours that was used by Mason and Dershin (A-3).

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o   A long half-life of 40 hours that was cited by Hickey (A-1).
        Actually, the indicated half-life was >40 hours, but 40 hours
        was used for calculation purposes.

All of the predictions satisfy the equal protection criterion. For two of the
half-lives, an increase in TLV-TWA is indicated for the novel schedule.
Essentially, no adjustment is predicted for the long half-life that yields the
slowest clearance rate. Benzene has both a fast and a slow clearance rate.

TABLE A-II. PREDICTED TLV ADJUSTMENTS FOR BENZENE IN
GASOLINE BASED ON THE HICKEY-REIST MODEL

$T_{1/2}$ (hours)	k (hours^{-1})	F_p	$(TLV-TWA)_n$*
3.3	0.21	1.325	13
7.7	0.09	1.28	13
40	0.017	0.98	10

* Approximate Values
$T_{1/2}$ = biological half life
k = clearance rate
Fp = adjustment factor
$(TLV-TWA)_n$ = exposure limit for the novel schedule;
        product of Fp and current TLV-TWA

When this situation occurs, Roach (A-2) suggests that the conservative
approach is to use the clearance rate that yields the lowest TLV for the novel
schedule, in this case the longest half-life. Based on this recommendation,
no adjustment in the TLV would be indicated. The example exposure profile is
below the TLV for the novel work schedule. In this case, the predicted ad-
justment conclusion agrees with the OSHA "no adjustment" criterion because
benzene is a Category 1C compound.

The assumptions of equality of peak body burden, constant exposure level
during a shift and periodic, equal duration work shifts permit a closed form
solution for the TLV adjustment factor. While these assumptions may be valid
in certain cases, the closed form approach does not reflect the variable

exposure profiles and extended work periods that are characteristic of marine operations. It is plausible that at some point in time these factors could result in a body burden that would temporarily exceed the corresponding accumulation from a TLV-TWA exposure.

To demonstrate this point, the first order differential equation for body burden accumulation as presented by Mason and Dershin (A-3) was integrated for an arbitrary exposure duration and initial body burden. The equation reflects the partitioning of the vapor between the air and body spaces. A similar expression was developed for clearance during non-exposure periods. By applying these equations in a piecewise fashion, it is possible to calculate the time-dependent body burden for variable exposure levels and durations within a shift. Extended work shifts and reduced rest periods are easily represented. It was assumed that the exposure concentration is constant over the sampling interval which is less than the duration of a 4-hour watch. As a boundary condition, the body burden at the beginning of the next time interval of interest was required to be equal to the burden at the end of the preceding interval.

The measured occupational exposure data in Figure A-1 were input to the formulation. This figure indicates that exposure commended with the beginning of a 4-hour watch. The body burden for this exposure profile is shown in Figure A-2 together with the accumulation that would be predicted for a constant exposure at the current TLV-TWA. An initial body burden of zero was assumed. The actual chemical substance that is reflected in the body burden profiles is unimportant. The relevant point is that the actual body burden temporarily exceeded that which would be predicted for a TLV-TWA exposure. The amount and duration of such temporary deviations may be important to the toxicologist in assessing the impact of the exposure environment.
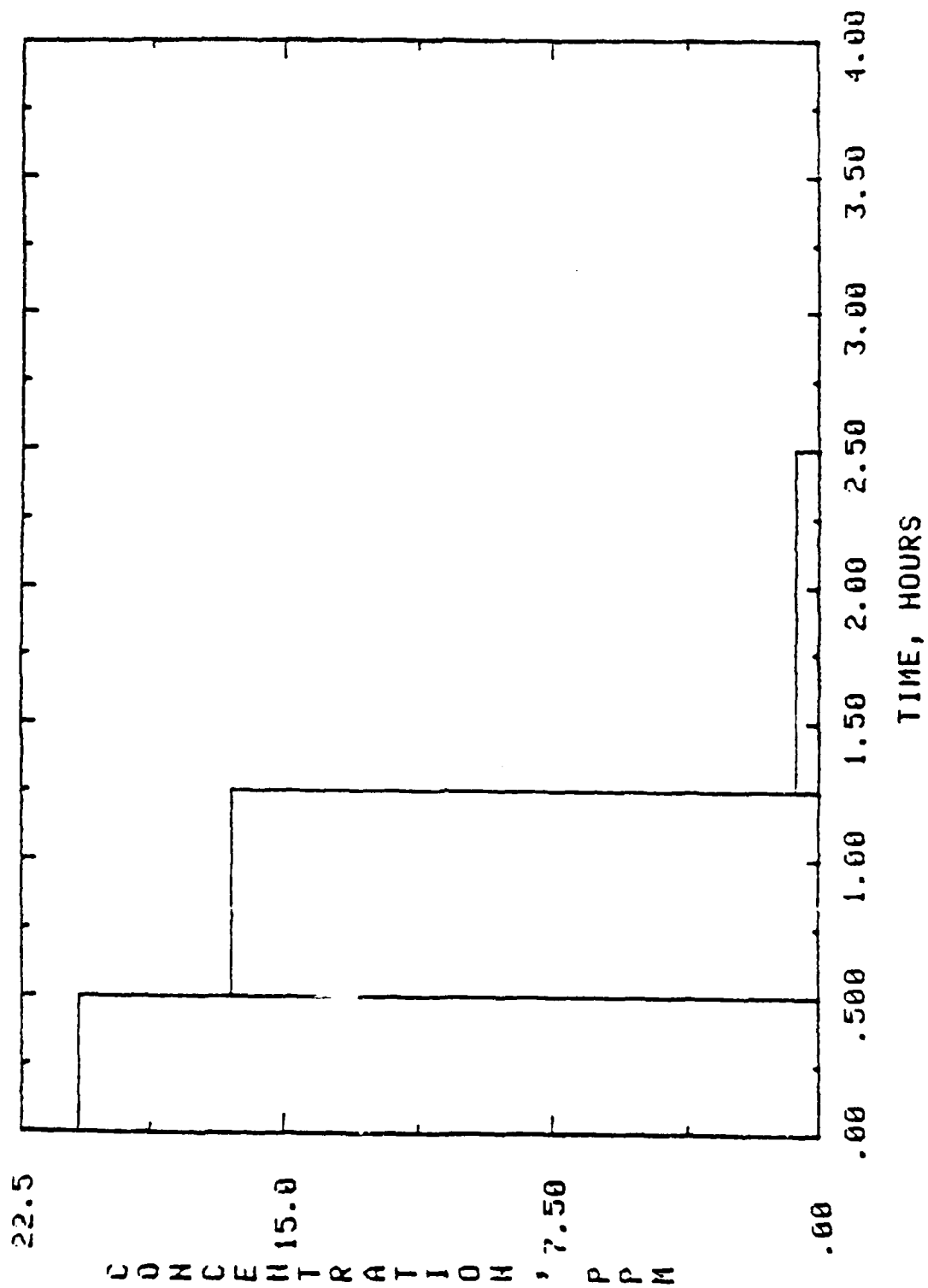
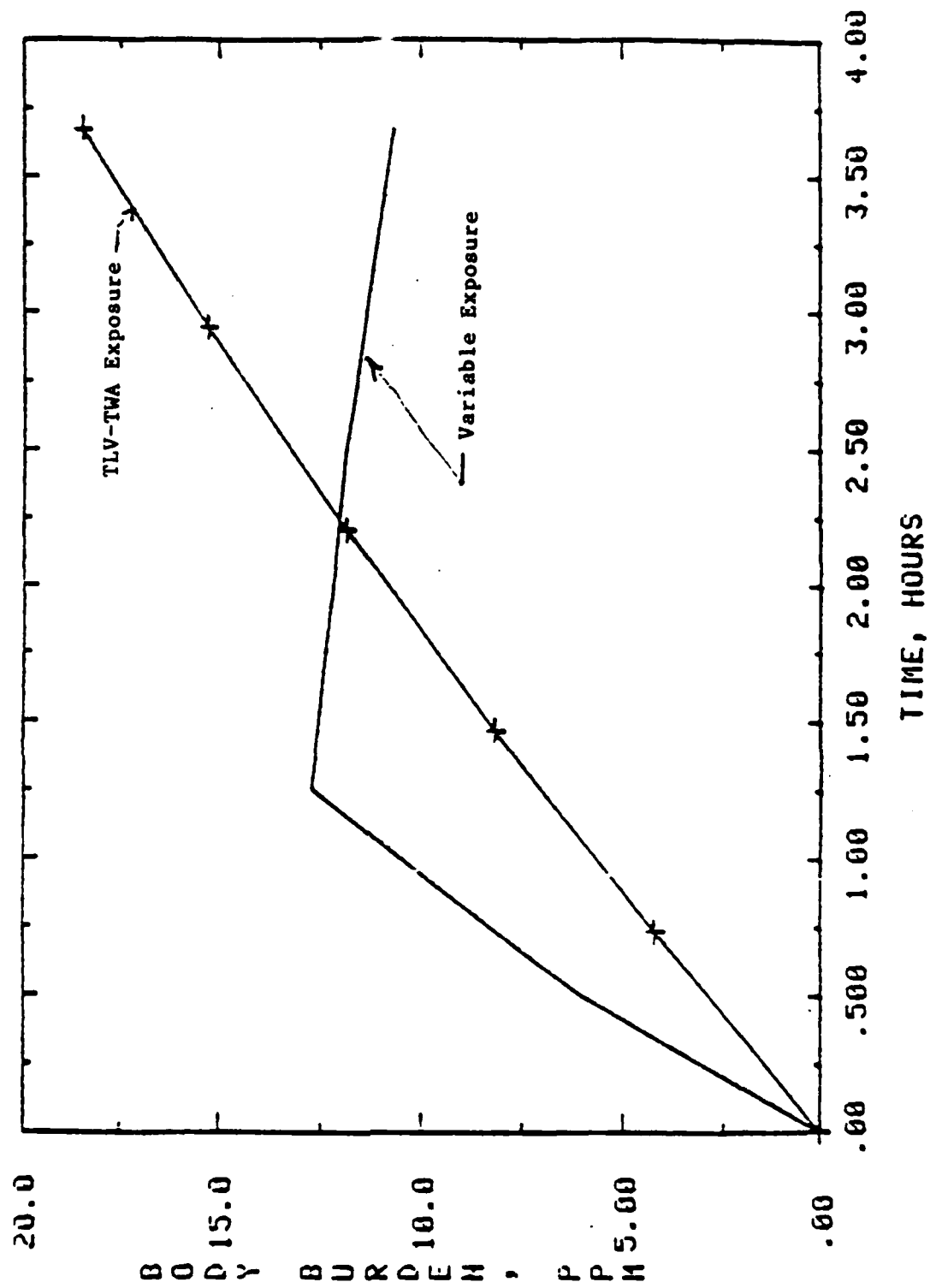FIGURE A-1. EXPOSURE CONCENTRATION TIME HISTORY

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FIGURE A-2. BODY BURDEN COMPARISON WITH TLV STANDARD

APPENDIX A REFERENCES

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